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The BULLETIN

American Society of Hospital Pharmacists

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DRUG EVALUATIONS

by the Council on Drugs of the American Medical Association

The following monographs and supplemental statements on drugs have been authorized by the Council on Drugs of the American Medical Association for publication and inclusion in *New and Nonofficial Drugs*. They are based upon the evaluation of available scientific data and reports of investigations. In order to make the material even more valuable, dosage forms and preparations of individual drugs have been added to the monographs. These dosage forms and preparations were not taken from material published in the *Journal of the American Medical Association* by the Council on Drugs; rather, they were obtained from such manufacturers' brochures, news releases, etc., which were available to us at the time of publication. An attempt has been made to make the list of dosage forms as complete as possible. However, no guarantee can be made that the list of preparations is complete and it is suggested that hospital pharmacists consult manufacturers' releases for additional dosage forms and preparations.

The issues of the *Journal of the American Medical Association* from which each monograph has been taken is noted under each monograph. Monographs in this issue of THE BULLETIN include those published in the *Journal* to August 1, 1957.

NOTICE

New and Nonofficial Remedies 1957 is now available from your local bookstore and from the publishers, J. B. Lippincott Company, Philadelphia, Pa. This 1957 edition contains monographs of drugs evaluated by the Council on Drugs of the American Medical Association and published in the Journal of the A.M.A. to October 1956. The index listed below contains those drugs evaluated and published between October 1, 1956 and August 1, 1957.

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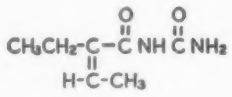
Ectylurea — Nostyn®

Ectylurea is 2-ethyl-*cis*-crotonylurea. The structural formula of ectylurea may be represented as follows:



Actions and Uses

Ectylurea produces mild depression of the central nervous system, an action it shares with other substituted urea compounds. In experimental animals, the drug exerts sedative effects from doses much lower than those required to produce hypnosis. It does not influence blood pressure, pulse, respiration, or gastric acidity and motility, nor does it produce skeletal muscle relaxation, analgesia, or anticonvulsant effects. Ectylurea is readily absorbed from the gastrointestinal tract, and approximately two-thirds of an orally administered dose appears in the urine as urea within 12 hours. The site of metabolic breakdown and the precise mechanism of action of this drug are not known.

From pharmacological considerations, the potential clinical usefulness of ectylurea as a sedative but not as a direct hypnotic might logically follow. Thus, the drug has been employed as a mild neurosedative or calming agent in the treatment of simple anxiety and nervous tension. Although few well-controlled investigations have been reported, it is the clinical impression of most observers that the drug exerts mild tension-relieving effects. These effects have been reported in adults in all age groups and hyperexcitable children with behavior problems. In some pediatric cases daily administration of the drug has resulted in diminution of restlessness and irritability. The drug is not a hypnotic per se but may promote sleep in some patients whose tension and anxiety are responsible for insomnia. Additional controlled clinical studies are necessary, however, to establish the ultimate usefulness of ectylurea as a calming agent. There is no evidence that the drug is of any benefit in alcoholic patients or those with frank psychoses.

On the basis of both laboratory and clinical reports, it would appear that the toxicity of ectylurea is extremely low. It has been administered in doses far in excess of therapeutic levels without adversely affecting hepatic function or the hematopoietic, renal, or cardiovascular systems. The margin of safety and dosage range for sedation is high. In clinical studies, the only side-effect encountered to date has been a skin rash, which appears in considerably less than 1% of patients.

Dosage

Ectylurea is administered orally. The optimal dosage has not been firmly established; amounts ranging from 0.15 to 0.3 Gm. three or four times daily may be employed, apparently without appreciable risk of toxicity.

Applicable commercial name: Nostyn.
Ames Comany, Inc., cooperated by furnishing scientific data to aid in the evaluation of ectylurea.
***J. Am. Med. Assoc.* 164:1093 (July 6) 1957.**

Preparations

Tablets Ectylurea (Nostyn) 0.3 Gm.

Isoflurophate — Use in Strabismus

The Council previously has described the ophthalmic use of a 0.1% solution in peanut oil of the potent irreversible cholinesterase antagonist isoflurophate (Floropryl) in the treatment of certain forms of glaucoma. The Council has evaluated additional evidence for its ophthalmic use as a 0.025% ointment in the treatment of glaucoma as well as in the management of accommodative (nonparalytic) convergent strabismus (esotropia). The use of either concentration of the drug in glaucoma is based upon its miotic action, whereas the use of only the lower concentration in nonparalytic esotropia is based upon its peripheral stimulatory action on the intraocular muscles of accommodation. The latter action, if pronounced, may provoke disabling ciliary spasm accompanied by unpleasant side-effects, which may interfere with the use of the drug. Such effects usually tend to diminish or disappear with continued therapy. The potent miotic effect of the drug, even with the use of the lower concentration in the treatment of nonparalytic esotropia, has been associated with the development of iris cysts, which may obscure vision. Iris cystic involvement usually is reversible after withdrawal of the drug and often can be obviated by administration of dosage at infrequent intervals. However, if the drug is not effective for maintenance therapy when instilled at dosage intervals of 48 hours or longer, its use is contraindicated. Iris cysts appear in a large proportion of children after some weeks or month of administration of the drug at shorter intervals. In such instances the drug should be abandoned in favor of other forms of therapy.

From available evidence the Council concluded that

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ophthalmic use of the 0.025% ointment is suitable in strabismus when visual acuity is approximately equal in both eyes (1) as a diagnostic agent to estimate the factor of accommodative effort commonly encountered in hypermetropic nonparalytic esotropia, and (2) as a therapeutic agent to reduce or overcome the excessive centrally stimulated accommodative effort by substitution of peripherally stimulated accommodation in such cases. The Council also found some evidence to indicate that, when esotropia is complicated by anisometropia or amblyopia, the 0.025% concentration may be used only in the more affected eye. In amblyopic esotropia, in which use of the drug in the more affected eye is combined with use of atropine in the fixating eye, care is necessary to deatropinize the latter as soon as the former is fixating, to avoid amblyopia in the originally fixating eye. The drug also is used after corrective surgery to overcome residual esotropia due to excessive accommodative effort. Orthoptic training is considered desirable before initiating corrective drug therapy because such training is difficult in the presence of drug-induced miosis. Drug therapy may supplant or supplement the use of glasses in patients with little or no astigmatism, particularly in very young children, in childhood where social activities or behavior problems interfere with their use, and in the transition from use of glasses to their abandonment.

The Council reaffirms the view that the drug is suitable only for ophthalmic use by conjunctival instillation, owing to its potentially profound systemic cholinergic effects; it may even be absorbed from accidental contact with the skin. Precautions are essential to avoid such contact, to wash away any of the drug accidentally spilled on the skin, and to prevent accidental ingestion by children or inadvertent injection of the drug into the tissues. Ophthalmic use is seldom if ever associated with systemic effects when the drug is used in the available concentrations according to the suggested dosage. Because the drug is rapidly hydrolyzed by water, care should be exercised to avoid washing the eye dropper with water or allowing it to come in contact with the conjunctival sac. The usual effective dosage of the 0.025% ointment in glaucoma is 1 drop (¼-in. extrusion from an ophthalmic tube container) in the affected eye every 8 to 72 hours. Bedtime administration is desirable, if feasible, to minimize blurring of vision. In the initial estimation and management of nonparalytic esotropia, the usual dose is not more than 1 drop or ¼ in. of the ointment in each eye daily at bedtime for two weeks. If the drug proves beneficial, the dosage interval should be lengthened to 48 hours and up to as little as once weekly, depending on the least amount required to maintain binocular fixation without abnormal convergence.

The Council voted to revise New and Nonofficial Drugs to describe the use of isoflurophate in the management of nonparalytic esotropia.

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., cooperated by furnishing scientific data to aid in the evaluation of this additional use of isoflurophate.

J. Am. Med. Assoc. ***164***:875 (June 22) 1957.

Meprobamate — Potential Hazards

Since its introduction almost two years ago, the tranquilizing agent meprobamate (Equanil, Miltown) has been received with considerable enthusiasm by the general public as well as by large segments of the medical profession. This widespread interest has been based primarily on the assumption that large doses of the drug can be administered with practically no side-effects. The original clinical investigations on meprobamate[1] indicated it to be an agent of extremely low toxicity over a wide range of dosage. These reports were based on observations in a relatively small number of patients. As the use of the drug has multiplied, however, it has become increasingly apparent that meprobamate is capable of producing a rather wide variety of side-effects and untoward reactions. Although no fatalities have been reported to date, some of these reactions are alarming and potentially hazardous. Hence, it seems advisable to apprise physicians of the possible adverse reactions to meprobamate.

Hypersensitivity reactions have occurred with sufficient frequency to indicate that these are definite and not infrequent complications of meprobamate therapy.[2] Dermal manifestations have included urticaria and diffuse maculopapular and erythematous skin rash, often accompanied by intense pruritus. Shaking chills and fever may also occur. Some patients have experienced these allergic-type reactions after single oral doses of as little as 0.4 Gm. In some cases, symptoms have been severe enough to require the administration of corticotropin or adrenocortical steroids. Since hypersensitivity reactions of this type have occurred in patients with no previous history of allergy or prior exposure to meprobamate, the drug should be administered cautiously to such patients and should be withdrawn at the first sign of a cutaneous eruption.

Acute nonthrombocytopenic purpura is another potentially serious type of hypersensitivity reaction to meprobamate. This has occurred in at least four patients to date.[3] Symptoms have included widespread purpuric, erythematous, and petechial dermatitis, peripheral edema, and fever. Platelet counts are not affected, but there is evidence of increased capillary permeability. Whether more serious complications would ensue if therapy were continued in such patients is not known. There is no evidence that meprobamate exerts an adverse effect on the hematopoietic system or is a causative agent in blood dyscrasia.

Several reports of acute meprobamate intoxication have been recorded.[4] In most instances these have resulted from deliberate ingestion of very large amounts of the drug, ranging from 6 to 38 Gm. None of these reported suicidal attempts have been successful, but severe central depression with alarming signs and symptoms has been observed. These include coma with shallow respiration, muscular weakness, absence of reflexes, and hypotension approaching shock-like levels. In the most severe cases, complete respiratory and vasomotor collapse have been reported. No definite antidote or regimen of therapy for overdosage has been devised. It is therefore important that meprobamate be prescribed with considerable discretion and in small quantities, if at all, in patients who may have suicidal tendencies. Physicians should also consider the possibility that meprobamate as well as the other tranquilizing drugs may increase such tendencies in agitated patients after its withdrawal.

There is also some evidence that meprobamate possesses habit-forming properties.[5] Withdrawal symptoms, including convulsions in some patients, have been observed when use of the drug has been discontinued abruptly after prolonged therapy. In such

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cases the drug should be withdrawn gradually. In addition to physical dependence, psychic dependence with a tendency toward excessive self-medication is undoubtedly created in certain patients. Some patients also may experience tolerance to the drug and, because progressively larger amounts of the drug may be required to maintain the therapeutic effect, the chances of acute intoxication are appreciably increased. Since the drug is intended primarily for those with basic emotional instability, cognizance of the possible occurrence of these psychic complications is requisite for intelligent therapy.

Drowsiness occurs in a substantial number of patients undergoing therapy with meprobamate, but this appears to be an accompaniment of its mild somnifacient action rather than a side-effect. Other reported, although rarely encountered, side-effects and untoward reactions include gastric discomfort, paradoxical reaction with extreme excitement, intestinal hyperperistalsis with abdominal cramping and flatulence, severe diarrhea with rice-water stools, palsy of extraocular muscles with diplopia, and generalized muscular paralysis.[2a]

The foregoing consideration of reported reactions to the drug is not intended to be construed as evidence that the usefulness of meprobamate is outweighed by its potential side-effects. It has been administered to a very large number of patients, and the actual percentage of serious adverse reactions, while unknown, is undoubtedly quite small. Accordingly, this report is intended to point out that side-effects and untoward reactions to meprobamate can and do occur and that the drug should be administered with the same discretion as other therapeutic agents.

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J. Am. Med. Assoc. 164:1332 (July 20) 1957.

Mumps Skin Test Antigen

MUMPS SKIN TEST ANTIGEN is a sterile suspension of killed mumps virus in isotonic sodium chloride solution, preserved with 1:10,000 thimerosal. The virus is grown in embryonated chicken eggs and is inactivated by ultraviolet light or formaldehyde. Mumps skin test antigen is tested for antigenicity, sterility, and safety according to specifications of the National Institutes of Health. Each cubic centimeter contains 20 complement-fixing units.

Actions and Uses

Mumps skin test antigen is used to detect specific skin hypersensitivity to the mumps virus. Thus, it may be employed to determine susceptibility to mumps or to confirm a tentative diagnosis of the disease. The development of skin sensitivity seems to require some time. Confirmation of a tentative diagnosis of mumps can be achieved only several weeks to months after onset of the disease. The skin test antigen generally should be used prior to vaccination in order to identify suitable nonimmune candidates for active immunization. Use of mumps vaccine or repeated skin tests do not seem to affect the skin reaction. Since mumps skin test antigen is prepared from the embryonic fluid of chicken eggs, its administration is absolutely contraindicated to persons giving a history of hypersensitivity to egg, chicken, or chicken feathers. If there is a negative history of hypersensitivity and a pseudo-positive reaction indicating hypersensitivity develops from a skin test, subsequent use of mumps vaccine is contraindicated.

Dosage

Mumps skin test antigen is administered intradermally in doses of 0.1 cc. The usual site of injection is the inner surface of the forearm; no control test is considered necessary. The injected area should be observed in 24 to 36 hours. If a control is used, it should be realized that reactions to the control usually do not fade before 48 hours; therefore, comparison with the specific antigen should not be made within this period of time.

Applicable commercial name: Mumps Skin Test Antigen.
Eli Lilly and Company cooperated by furnishing scientific data to aid in the evaluation of mumps skin test antigen.

J. Am. Med. Assoc. 164:874 (June 22) 1957.

Preparations

Injection Mumps Skin Test Antigen 1 ml. (10 tests) vials.

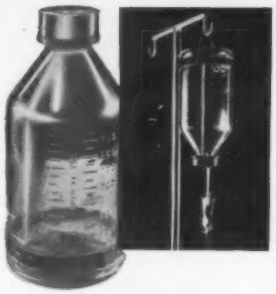
Mumps Vaccine

MUMPS VACCINE is a sterile supension of mumps virus, grown in embryonated chicken eggs, inactivated by ultraviolet light or formadehyde, and preserved with 1:10,000 thimerosal. Mumps vaccine is standardized for potency and antigenicity according to specifications of the National Institutes of Health.

Actions and Uses

Mumps vaccine is used for active immunization against mumps. Detectable increases in antibody titer are apparent within one week after subcutaneous injection of the vaccine, but the duration of this actively acquired immunity is uncertain. Current evidence suggest that protection against the disease does not persist for longer than a year after vaccination. Thus, mumps vaccine does not confer the same degree of immunity as a naturally acquired infection. Although the vaccine may be given within two to three days after exposure, no information is at hand to indicate that the vaccine successfully aborts a clinical case of mumps or alters the course of the subsequent disease. Hence

1.



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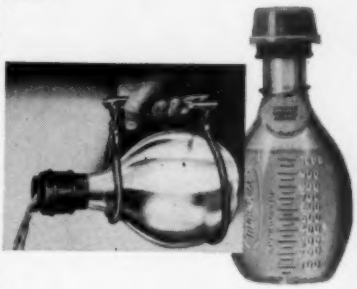

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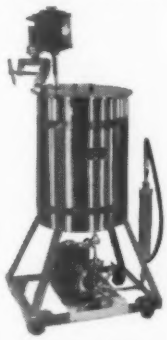

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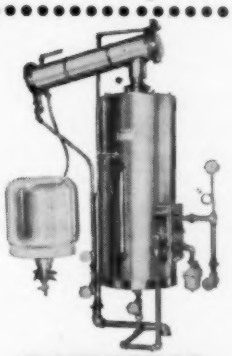

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vaccination is indicated only in certain restricted circumstances as a prophylactic measure before exposure. Since the clinical course of and sequelae to mumps are usually not severe in children and since a naturally acquired infection generally confers lifelong immunity, the use of the vaccine in children is justified only as a means of preventing widespread epidemics in those situations in which large numbers of children are kept in close proximity for long periods, as, for example, in orphanages or boarding schools. It is not advisable for children in isolated circumstances. The vaccine may be employed prophylactically in adults when antibody titers or skin tests indicate a lack of immunity. If a vaccination is administered before exposure in such cases, the patient is less likely to develop clinical mumps and, hence, the potentially serious complications of orchitis and meningoencephalitis. As in the younger age group, vaccination of adults should generally be restricted to individuals who live in closely segregated populations where epidemic parotitis and its numerous sequelae may become a serious problem. Such groups are exemplified by military personnel, nurses, medical students, and institutionalized or hospitalized patients. Fortifying or booster injections 6 to 12 months after primary immunization are desirable if protective antibody titers are to be maintained.

Since mumps vaccine is prepared from the embryonic fluid of chicken eggs, its administration is absolutely contraindicated to persons giving a history of hypersensitivity to egg, chicken, or chicken feathers. If there is a negative history of hypersensitivity and a pseudo-positive reaction indicating hypersensitivity develops from a skin test, subsequent use of mumps vaccine is contraindicated.

Dosage

Mumps vaccine is administered subcutaneously. The immunizing dose for children and adults consist of two injections of 1 cc. each. The optimal interval between injections is not known, but periods of one to four weeks are usual. A booster dose of 1 cc. may be indicated after 6 to 12 months.

Applicable commercial name: Mumps Vaccine.

Lederle Laboratories Division, American Cyanamid Company; and Eli Lilly and Company cooperated by furnishing scientific data to aid in the evaluation of mumps vaccine.

J. Am. Med. Assoc. 164:875 (June 22) 1957.

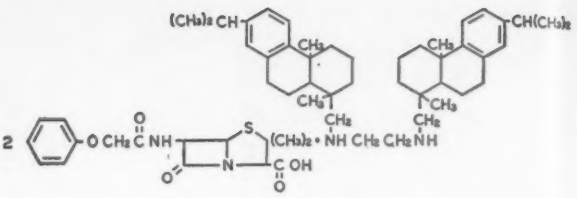
Preparations

Injection Mumps Vaccine 2 ml. (1 immunization) and 10 ml. (5 immunizations) vials.

Hydrabamine Phenoxymethyl Penicillin

Compocillin-V® Hydrabamine

HYDRABAMINE PHENOXYMETHYL PENICILLIN is hydrabamine penicillin V. A mixture of crystalline phenoxymethyl penicillin salts consisting chiefly of the salt of N,N′-bis-(dehydroabietyl) ethylenediamine, with smaller amounts of the salts of the dihydro- and tetrahydroderivatives. The structural formula of hydrabamine phenoxymethyl penicillin may be represented as follows:



Actions and Uses

Hydrabamine phenoxymethyl penicillin (hydrabamine penicillin V) has the same actions and uses as phenoxymethyl penicillin. (See the monograph on phenoxymethyl penicillin in New and Nonofficial Remedies.) It is water-insoluble, and, as such, is used in the form of a stable, aqueous supension for oral administration. The salt dissociates in the gastrointestinal tract to release phenoxymethyl penicillin for prompt absorption, as indicated by the penicillin blood level pattern, which is similar to that obtained with phenoxymethyl penicillin or its sodium salt. Animal studies indicate that the hydrabamine base portion of the compound is chiefly unabsorbed when given by the oral route; up to 90% is recovered in the feces, with less than 1% found in the urine. Fecal excretion of the base is not influenced significantly by the normal intestinal flora.

Dosage

Hydrabamine phenoxymethyl penicillin is administered orally. The usual dose for acute infections is 180 mg. (300,000 units) every four to six hours; subsequent dosage should be regulated according to therapeutic response. For continuous prophylaxis in rheumatic fever, 180 mg. (300,000 units) is administered daily. A total of 180 to 360 mg. (300,000 to 600,000 units) a day in four divided doses for 10 days should be given to patients with streptococcic infections who have had rheumatic fever or show signs of rheumatic heart disease. Although dosage may be reduced for children according to age or weight, it is considered wise to give children a somewhat higher dosage than strict ratios based on age or weight would suggest. Children 12 years of age or over will usually tolerate adult doses without ill-effects.

Applicable commercial name: Compocillin-V Hydrabamine.

Abbott Laboratories cooperated by furnishing scientific data to aid in the evaluation of hydrabamine phenoxymethyl penicillin.

J. Am. Med. Assoc. 164:1094 (July 6) 1957.

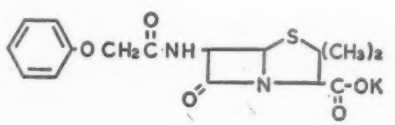
Preparations

Suspension, Oral, Hydrabamine Phenoxymethyl Penicillin (Compocillin-V) 180 mg. (300,000 units) per 5 ml.; 40 ml. and 80 ml. bottles.

Potassium Phenoxymethyl Penicillin

Compocillin-V® Potassium

POTASSIUM PHENOXYMETHYL PENICILLIN is potassium penicillin V. The structural formula of potassium phenoxymethyl penicillin may be represented as follows:



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GREATER SAFETY "Its [Nesacaine] chief virtue appears to be its relative non-toxicity. [No reactions in 350 anesthetics.]"[2]

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MAXIMAL EFFICACY "Nesacaine . . . was found effective . . . it would appear to be the best agent for use as a local anesthetic."[2]

1. Colavincenzo, J. W., and others: Pennsylvania M. J. 59:338 (March) 1956.
2. Ansbro, F. P., and Furlong, R. E.: Adelphi Hosp. Bull. 15:2 (May) 1957.
3. Foldes, F. F., and McNall, P. G.: Anesthesiology 13:287 (May) 1952.

In 30 cc multiple dose vials—
1% Nesacaine for infiltration and field block
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PNE-72

Actions and Uses

Potassium phenoxymethyl penicillin has the same actions and uses as phenoxymethyl penicillin. (See the monograph on phenoxymethyl penicillin in New and Nonofficial Remedies.)

Dosage

Potassium phenoxymethyl penicillin is administered orally in the same dosage as that for phenoxymethyl penicillin.

Applicable commercial name: Compocillin-V Potassium Abbott Laboratories cooperated by furnishing scientific data to aid in the evaluation of potassium phenoxymethyl penicillin.

J. Am. Med. Assoc. 164:1094 (July 6) 1957.

Preparations

Tablets Potassium Phenoxymethyl Penicillin (Compocillin-V) 125 mg. (200,000 units) and 250 mg. (400,000 units).

Phenylbutazone — Additional Use

The Council has evaluated the usefulness and safety of phenylbutazone (Butazolidin) for the treatment of the chronic joint disease, osteoarthritis. Although this anti-inflammatory agent exerts an appreciable analgesic effect, its clinical usefulness is limited by the high incidence of side-effects and untoward reactions, the most serious of which are leukopenia and agranulocytosis. When employed cautiously, however, it has proved useful as an analgesic in certain musculoskeletal disorders. Thus, phenylbutazone has been described previously as useful in the treatment of gouty arthritis, and, to a lesser extent, psoriasis with arthritis, ankylosing spondylitis, rheumatoid arthritis, peritendinitis, capsulitis, bursitis, and acute arthritis of the shoulder joint. On the basis of additional evidence, the Council concluded that the drug may also be used in certain cases of osteoarthritis. Because of its toxicity, phenylbutazone probably should rarely be considered for therapy of this relatively benign chronic condition. Hence, its use should be restricted to the treatment of acute exacerbations of symptoms in patients who fail to respond to more conservative forms of therapy. These include rest, a careful explanation of the condition with reassurance, weight reduction when indicated, local heat or other physical measures, and administration of salicylates. If the drug is administered on an outpatient basis, patients should be advised of the possible occurrence of side-effects and untoward reactions; moreover, the physician should be prepared to follow each case carefully with particular attention to the peripheral blood cell count. Hence, employment of phenylbutazone for osteoarthritis is justified only in restricted circumstances and under the most carefully controlled conditions. (See the monograph on phenylbutazone in New and Nonofficial Remedies.)

Although the manufacturer of phenylbutazone has not proposed its use in the adjunctive management of acute thrombophlebitis, a number of reports on this subject were reviewed. On the basis of these, the Council concluded that there is insufficient evidence at the present time to determine the efficacy or safety of the drug for this condition.

The dosage of phenylbutazone for the treatment of osteoarthritis varies according to the response of the patient and the appearance of side-effects. As a general guide, an average initial dose of 0.6 Gm. daily, administered for one week, is considered adequate to determine the therapeutic effect of the drug. In the absence of a favorable response, further therapy should be discontinued. When improvement is obtained, the dosage should be gradually decreased to the minimum effective level. An effective maintenance dosage may be as low as 0.1 to 0.2 Gm. per day. Dosage for use in acute thrombophlebitis has not been established.

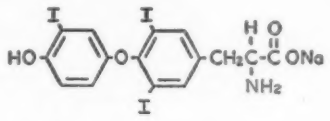
The Council voted to amend New and Nonofficial Drugs accordingly to describe the use of phenylbutazone in osteoarthritis.

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, cooperated by furnishing scientific data to aid in the evaluation of this additional use.

J. Am. Med. Assoc. 164:1095 (July 6) 1957.

Sodium Liothyronine — Cytomel® Trionine®

SODIUM LIOTHYRONINE is sodium L-triiodothyronine. Sodium L-4-(iodo-4-hydroxyphenoxy)-3,5-diiodophenylalanine. The structural formula of sodium liothyronine may be represented as follows:



Actions and Uses

Liothyronine, the physiologically active isomer of triiodothyronine, is approximately twice as active as the racemic (DL-) form. The drug differs in chemical structure from thyroxin only in the absence of one iodine atom at position 5. It produces all of the qualitative metabolic and clinical effects of desiccated thyroid and thyroxin but differs quantitatively in being much more rapid in action and about three to four times as potent as an equal amount of levothyroxine (L-thyroxine). Liothyronine has been isolated in minute amounts from the thyroid gland and the blood plasma; however, sodium liothyronine is prepared synthetically. The thyroid gland itself is not believed to be a principal site of elaboration of this substance; recent studies have demonstrated that levothyroxine is converted to liothyronine in various peripheral tissues. These studies suggest the possibility that levothyroxine, the principal secretion of the thyroid gland, becomes active at the cellular level only after deiodination to the triiodo form, liothyronine. The metabolically active substance is then believed to be absorbed directly by the target cells, thus eliminating the latent period ordinarily required for the deiodination of levothyroxine. Although this concept will require further study for ultimate substantiation, it offers a plausible explanation for the potency, rapid onset, and the short duration of the action of liothyronine after cessation of therapy.

Sodium liothyronine is absorbed readily from the gastrointestinal tract. It is rapidly cleared from the blood stream and is more loosely bound to plasma proteins that is thyroxin; hence, oral administration does not appreciably elevate the levels of protein-bound iodine. Little is known about the metabolism of liothyronine in the peripheral tissues except that iodine is liberated. Some of this iodine is excreted in the feces via the bile; the remainder is transported to

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Organon INC.
ORANGE, N. J.

the thyroid, where it is synthesized to thyroxin and stored as thyroglobulin.

Sodium liothyronine is effective for the treatment of hypothyroidism. It may therefore be employed as initial therapy or as an adequate replacement for thyroxin or desiccated thyroid in the treatment of primary and secondary myxedema, cretinism, and occult hypothyroidism. Clinical diagnosis of the latter condition should be confirmed by the usual laboratory findings of lowered protein-bound iodine value, low radioactive iodine uptake, and low basal metabolic rate. There is also evidence that sodium liothyronine is of value in the treatment of simple, nontoxic goiter. In certain circumstances, the rapid onset and short duration of action of the drug offer definite advantages over the older thyroid preparations. Thus, effects of the drug subside more rapidly once therapy has been discontinued, and a more rapid therapeutic effect may be achieved when deficiency symptoms are unusually severe. On the other hand, the more frequent administration of the drug required for continuous therapy may be disadvantageous in the long-term management of such conditions as myxedema. There is, however, adequate evidence that liothyronine is not only a satisfactory substitute for thyroxin and desiccated thyroid in the treatment of hypothyroidism but is also capable of producing satisfactory responses in some patients whose conditions are refractory to these drugs.

Sodium liothyronine has been employed for the treatment of a syndrome known as metabolic insufficiency. This is said to be characterized by such complaints as lethargy, easy fatigability, dry hair and skin, obesity, nervousness, irritability, emotional instability, sensitivity to cold, headache, ill-defined aches and pains, facial puffiness, water retention, diminished sexual potency in the male, and menstrual irregularity and dysmenorrhea in the female. Although these diverse signs and symptoms do not necessarily identify a specific disease entity, they may be related to a nonthyroidal deficiency of metabolic-regulating principle(s) at the cellular level. Thus, it is believed that, in certain patients with normal thyroid function as measured by protein-bound iodine values and radioactive iodine uptake, there is an inability of the peripheral target tissues to utilize thyroxin or to convert it into the more active form, liothyronine. In such patients, the basal metabolic rate may be low, and no improvement as evidenced by symptomatic response or elevation of basal metabolic rate can be obtained by administration of thyroxin or thyroid extract. Some patients with the foregoing clinical and laboratory findings have improved after administration of sodium liothyronine. Although such observations have fostered the concept of metabolic insufficiency and although a clinical syndrome of euthyroid hypometabolism may exist, it still must be demonstrated that patients with nonmyxedematous hypometabolism are unequivocally benefited by sodium liothyronine. It should also be borne in mind that the signs and symptoms of this "syndrome" may be confused with many organic or functional disorders and that a beneficial effect may follow the administration of placebos in such conditions. Likewise, a depressed basal metabolic rate may be seen in conditions entirely unrelated to hypometabolism, as for example in adrenal cortical hypofunction (Addison's disease) or nephrosis. Thus, the use of liothyronine for so-called metabolic insufficiency should be reserved for those patients who present the clinical picture of hypothyroidism, including a low basal metabolic rate. The indiscriminate trial of this drug to relieve such vague symptoms as physical and mental sluggishness, irritability, depression, and nervousness is not justified.

Sodium liothyronine, as well as the older thyroid preparations, has been used empirically for the treatment of male infertility. There is some evidence that liothyronine, in contrast to thyroxin, effects an increase in sperm count and motility. Whether this effect improves fertility is not yet known. Additional controlled studies are therefore necessary to assess more fully the possible value of the drug in this condition.

Sodium liothyronine has also been used for the treatment of such gynecologic disorders as amenorrhea, premenstrual tension, and dysmenorrhea. In certain cases, the drug produces decidedly beneficial effects in the regulation of menstrual periods, particularly in young women. Whether these patients represent cases of so-called metabolic insufficiency or true hypothyroidism is unknown. In many instances, beneficial effects have been noted in patients who seem metabolically active and who present no clinical or laboratory evidence of thyroid insufficiency. Ultimate evaluation of sodium liothyronine for these purposes is further complicated by the poorly understood interrelationships between the hormonal, metabolic, and psychological factors involved in normal menstruation. However, since sodium liothyronine is a more rapidly acting form of thyroid hormone, its discriminate administration in carefully selected cases may be justified in an attempt to establish menstrual regularity.

Because of its rapid onset of action, symptoms of overdosage of sodium liothyronine such as tachycardia, excitability, or hyperhidrosis appear promptly, generally within 24 to 48 hours. The evanescent action of the drug, however, allows these unpleasant symptoms to subside within a similar period after discontinuation of medication. Sodium liothyronine should be used with extreme caution in the presence of angina pectoris, cardiovascular disorders, or ischemic states. It is contraindicated in patients with adrenal insufficiency, hypopituitarism, hypogonadism, or nephrosis.

Dosage

Sodium liothyronine is administered orally and dosage is expressed in micrograms. Initial dosage should be low and may be followed by small increases at weekly or biweekly intervals. The drug is administered in single or divided daily doses.

For the treatment of hypothyroid states, the usual initial dose for adults is 5 to 25 mcg. daily. Dosage is then increased at one-to-two-week intervals in small increments until a satisfactory response has been obtained. Maintenance requirements vary according to the severity of the hypothyroidism and the individual response. In overt myxedema, the recommended initial dose for adults is 5 mcg. daily, and the usual maintenance dose is 50 to 100 mcg. daily. In occult hypothyroidism, the usual initial dose is 25 mcg. daily; the usual maintenance dose is 25 to 75 mcg. daily. For nontoxic goiter, therapy is initiated with 5 mcg. daily; the usual maintenance dose is 25 to 75 mcg. daily. If sodium liothyronine is to be substituted for thyroxin or desiccated thyroid in athyreotic individuals, use of the latter agents should be discontinued one to two weeks before initiating liothyronine therapy.

Dosages that have been employed for adults in the syndrome known as metabolic insufficiency and in the treatment of male infertility and gynecologic disorders range from 5 to 25 mcg. daily initially, and from 25 to 75 mcg. daily for maintenance. For male infertility,

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and the
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multi-spectrum potentiated therapy . . . buffered for higher, faster antibiotic levels ...adds new certainty in antibiotic therapy ... *particularly for that 90% of the patient population treated at home or office when susceptibility testing is* not *practical*—

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SIGNEMYCIN† CAPSULES—250 mg. (oleandomycin 83 mg., tetracycline 167 mg.), bottles of 16 and 100; 100 mg. (oleandomycin 33 mg., tetracycline 67 mg.), bottles of 25 and 100.

SIGNEMYCIN FOR ORAL SUSPENSION—1.5 Gm., 125 mg. per 5 cc. teaspoonful (oleandomycin 42 mg., tetracycline 83 mg.), mint flavored, bottles of 2 oz.

SIGNEMYCIN INTRAVENOUS—500 mg. vials (oleandomycin 166 mg., tetracycline 334 mg.), and 250 mg. vials (oleandomycin 83 mg., tetracycline 167 mg.); buffered with ascorbic acid.

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maintenance doses are usually in the lower range. However, until the usefulness of the drug in these conditions is established, the dosage used for such purposes should be regarded as tentative.

For all indications, dosage should be proportionately reduced for infants and children and for geriatric patients.

Applicable commercial name: Cytomel.

Smith, Kline & French Laboratories cooperated by furnishing scientific data to aid in the evaluation of sodium liothyronine.

J. Am. Med. Assoc. 164:972 (June 29) 1957.

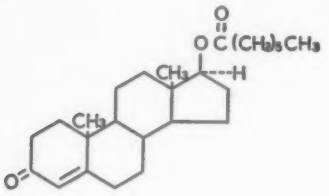
Preparations

Tablets Sodium Liothyronine (Cytomel) 5 mcg. and 25 mcg.

Tablets Sodium Liothyronine (Trionine) 5 mcg., 25 mcg., and 50 mcg.

Testosterone Enanthate — Delatestryl®

TESTOSTERONE ENANTHATE is Δ^4-androstene-17β-heptanoate-3-one.—The structural formula of testosterone enanthate may be represented as follows:



Actions and Uses

Testosterone enanthate has the same androgenic actions and uses as testosterone and its other esters. (See the general statement on testes in New and Nonofficial Remedies.) Administered as a solution in oil, the drug exerts a prolonged action. After a single intramuscular injection, detectable effects persist for a period of three to four weeks. Thus, testosterone enanthate is useful for androgen therapy when a prolonged action is desired. Its use is subject to the same precautions and contraindications as other androgenic agents.

Dosage

Testosterone enanthate is administered by deep intragluteal injection as a sterile solution in sesame oil containing 0.2 Gm. per cubic centimeter. The usual dosage ranges from 0.1 to 0.4 Gm. given at intervals of two to four weeks, depending on the condition being treated, prior androgen therapy, and individual response. For example, 0.2 to 0.4 Gm. every three to four weeks is considered adequate for the treatment of hypogonadism in the male. In cryptorchidism, doses of 0.1 to 0.2 Gm. every three to four weeks may be tried, providing no obstructive anatomic lesion exists. Single doses of 0.2 to 0.4 Gm. are injected to induce endometrial atrophy in menorrhagia; subsequently, doses of 0.1 to 0.2 Gm. one week before the expected onset of menstruation are administered. For postpartum breast engorgement and suppression of lactation, 0.1 to 0.2 Gm. is injected as soon as delivery is completed. The drug may be tried for the palliation of advanced mammary carcinoma; dosage should be adjusted according to response, but amounts of 0.2 to 0.4 Gm. every two weeks are usual. Because testosterone enanthate stimulates protein and bone anabolism, doses of 0.2 to 0.4 Gm. every three to four weeks have been suggested for osteoporosis in conjunction with appropriate supplemental measures. Further critical research is needed to demonstrate the ultimate utility of the drug when employed exclusively as an anabolic agent in other conditions. Due to its prolonged action, injections of testosterone enanthate more often than every two weeks are rarely indicated regardless of the condition being treated.

Applicable commercial name: Delatestryl.

E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, cooperated by furnishing scientific data to aid in the evaluation of testosterone enanthate.

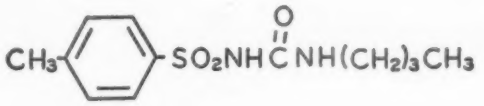
J. Am. Med. Assoc. 164:1094 (July 6) 1957.

Preparations

Injection Testosterone Enanthate (Delatestryl) 200 mg. per ml.; 1 ml. and 5 ml. vials.

Tolbutamide — Orinase®

TOLBUTAMIDE is 1-butyl-3-*p*-tolylsulfonylurea. The structural formula of tolbutamide may be represented as follows:



Actions and Uses

Tolbutamide, an orally active hypoglycemic agent, has been found useful for the management of diabetes mellitus in carefully selected patients. It is classified chemically as a sulfonamide derivative; that is, it contains an $-SO_2N<$ group. However, the drug is not a sulfanilamide derivative, since it contains a methyl group ($-CH_3$) at the para position of the benzene ring rather than the characteristic amino group ($-NH_2$). Since the latter group ($-NH_2$) is present in practically all sulfonamide derivatives used in the treatment of infection and is considered of significant importance for bacteriostatic effect, tolbutamide is, as might be expected, devoid of antibacterial action. The outstanding pharmacological effect of orally or parenterally administered tolbutamide is a lowering of the blood sugar level. This has been observed in all species of laboratory animals studied and in human patients, both without and, in favorable cases, with diabetes mellitus. In nondiabetic patients, the drug produces a rapid fall in the blood sugar level which is most pronounced within one hour after oral administration. In responsive diabetic patients, however, this effect is much more gradual; ordinarily, a period of five to eight hours elapses before the blood sugar level reaches a minimum. There appears to be no rigid dose-response relationship with orally administered tolbutamide, since in humans, amounts in excess of 3.0 Gm. usually induce no greater fall in blood sugar level than do doses of 3.0 Gm. or less. Hence, the likelihood of acute hypoglycemic reactions is less with administration of tolbutamide than with insulin.

The mechanism by which tolbutamide reduces the blood sugar level is not completely understood. There

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in less time

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"Intravenous protein feeding when properly used, not only does not compete with oral feeding, it actually encourages and facilitates resumption of the normal method of eating temporarily interrupted by surgical or other disease."*

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. . . 112.5 grams of protein
. . . all essential electrolytes
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For further information about Amigen 800 write to Parenteral Products, Mead Johnson, Evansville 21, Ind.

*Elman, R.: Protein Needs in Surgical Patients, J. Am. Dietetic Assn. 32:524 (June) 1956.

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is, however, one factor relative to the mode of action that has been conclusively established—the drug will not lower the blood sugar level in the complete absence of pancreatic beta cells. Thus, it appears certain that the presence of a sufficient number of insulin-producing islets of Langerhans is essential for the elicitation of a hypoglycemic effect. It also has been shown that the major metabolic effects of insulin, such as the greater utilization of glucose by muscle and the promotion of lipogenesis, do not seem to be influenced by tolbutamide in the absence of endogenous insulin. In the light of present knowledge, therefore, the most favored hypothesis is that tolbutamide acts by eliciting insulin secretion from the beta cells. To what extent other factors, such as a potentiation of insulin action or a decreased metabolic destruction of insulin, mediate the action of tolbutamide is not known. From all known facts, however, and without definitive proof of mechansim of action, it is already clear that tolbutamide cannot in itself be considered an orally given insulin, nor is it a substitute for insulin in the absence of a functioning source of endogenous insulin.

Tolbutamide is absorbed rapidly from the gastrointestinal tract. The drug is detectable in the plasma within one hour after oral administration, and peak plasma levels are reached after three to four hours. In contrast to the bacteriostatic "sulfa drugs," tolbutamide is not acetylated. Instead, it undergoes oxidation, presumably in the liver, to an inactive carboxyl derivative. Excretion of the drug is rapid; as much as 75% of an orally administered dose appears in the urine as the inactive metabolite within 24 hours. Because this excretion product is readily soluble in acid urine, crystalluria, hematuria, and calculi are not serious problems during therapy with tolbutamide. The urinary metabolite does, however, interfere with the usual tests for albuminuria. Hence, special procedures must be employed to distinguish between true and pseudo-positive tests for albumin in the urine.

In certain carefully selected patients, tolbutamide is capable of controlling the manifestations of diabetes mellitus without the use of insulin. Although the efficacy or safety of the drug does not exceed that of insulin, the drug offers the obvious advantage of being effective when given orally. It should be emphasized that not all diabetic patients are suitable candidates for therapy with this agent. Extensive clinical trials have adequately demonstrated that its usefulness is restricted to patients with uncomplicated diabetes mellitus of the stable type variously described as relatively mild adult maturity-onset, or nonketotic which cannot be adequately controlled by dietary restrictions alone. Therapy is considered successful if there is an adequate drop in blood sugar level, a diminution in glycosuria, and a disappearance of such symptoms as pruritus, polyuria, polyphagia, and polydipsia. Because of a gradual and sustained effect on the blood sugar level, a single oral dose of tolbutamide appears to be capable of providing, in responsive patients, a better 24-hour control of the blood sugar level than is possible with a single injection of insulin. Once patient responsiveness is established, maintenance therapy with tolbutamide is usually accompanied by a lower incidence of acute hypoglycemic reactions than when insulin is employed.

Rational therapy with tolbutamide demands that the physician thoroughly acquaint himself with its established indications, its limitations, and the proper criteria for selecting candidates for therapy. As already indicated, the essential prerequisite for determining patient eligibility is that the diabetes be adult or maturity-onset in character and not controllable by dietary restriction. The patient most likely to respond satisfactorily to the drug is one in whom the disease is relatively mild and stable and who has developed diabetes sometime after the age of 30. In general, the longer the diabetes has been known to exist, the lower the incidence of responsiveness to tolbutamide. Thus, in the maturity-onset group of patients, the earlier the diabetic state can be diagnosed and treated, the better the chances for satisfactory control with tolbutamide. The severity of the disease also influences the responsiveness to the drug; the higher the insulin requirement, the less likelihood of successful conversion to tolbutamide. This is especially true if the diabetes is severe enough to require 40 or more units of insulin per day. Not all diabetic patients who fulfill the above criteria respond adequately to tolbutamide. As a further aid to prognosticate response to the drug, there are at present two indexes that have a fair degree of predictive reliability. In general, patients who report a history of diabetic coma or those who develop ketonuria within 24 hours after withdrawal of insulin rarely, if ever, achieve satisfactory control with tolbutamide; indeed, its use in these patients may be dangerous without assurance of prompt adequate treatment if such complications occur. The final determination of responsiveness to the drug lies in the result of a therapeutic trial for a period of not more than five to seven days in conjunction with a gradual withdrawal of insulin. If there is absence of ketonuria plus a satisfactory reduction in the blood sugar level and glycosuria during the trial period, the patient may be assumed to be responsive to the drug. Cautious continuation of therapy is then indicated. If, on the other hand, the patient develops ketonuria or glycosuria, shows an unsatisfactory lowering or persistent elevation of the blood sugar level, exhibits serious side-effects, or fails to obtain subjective or objective clinical improvement, he must be considered unresponsive to the drug. In such cases, further therapy should be discontinued and use of insulin reinstated in the former dosage. Since the chief advantage of tolbutamide over insulin lies in its effectiveness when given orally, there is no point in tolbutamide-insulin therapy, even if such therapy might drastically reduce insulin requirements. Thus, unless tolbutamide alone can effectively control the disease, it should not be used at all.

Tolbutamide is of no value and is contraindicated in patients with juvenile or growth-onset types of diabetes mellitus. If the disease develops in a patient under 20 years of age, a therapeutic trial is not considered worthwhile. The drug likewise has no place in the treatment of the unstable or "brittle" type of diabetes, regardless of the age of the patient. Initiation or continuation of therapy with tolbutamide is contraindicated in patients with adult or maturity-onset type of diabetes when complicated by ketosis, acidosis, diabetic coma, infections, severe trauma, major surgical procedures, gangrene, Raynaud's disease, liver disease, or serious impairment of renal or thyroid function. The need for insulin, even though temporary, is indispensable during the course of such complications.

Education of the diabetic patient is essential for the safe and efficacious use of tolbutamide. As with the insulin-treated patient, the diabetic receiving tolbutamide should realize, first and foremost, that his medication controls rather than cures his disease and that its daily administration will probably be necessary throughout the rest of his life. Such patients should

NEW INTRAMUSCULAR IRON PROVIDES PRECISION THERAPY, PROMPT RESPONSE

IMFERON,® the new intramuscular iron-dextran complex, was introduced to American hematologists at the Sixth International Congress of the International Society of Hematology held in Boston, August 27 to September 1, 1956. Recent experience from over 6 million injections has shown that this iron preparation is easy to administer, notably free from toxic effects, quickly absorbed and productive of rapid hematologic and clinical improvement. It has been termed "...the only therapeutically effective iron preparation for intramuscular use...."[1]

IMFERON meets the need for a safe, effective agent when parenteral iron is preferable for patients with iron deficiency anemia who are resistant or intolerant to oral iron, those with depleted iron reserves and those who require rapid restoration of hemoglobin, *e.g.*, last trimester of pregnancy.

Previous parenteral iron preparations were unsatisfactory because of toxicity, pain on injection, or because they contained insufficient iron. IMFERON contains the equivalent of 5 per cent elemental iron. It is more stable than iron saccharate both *in vitro* and *in vivo* and does not precipitate in plasma over a wide pH range. It is isotonic with tissue fluids and has a pH of 5.2 to 6.0.[1] Utilization for hemoglobin formation is almost quantitative.

Precision Therapy with IMFERON: Before treating a patient with IMFERON, total iron requirement is calculated by formula or determined from a convenient dosage chart. Then appropriate amounts of IMFERON are injected daily or every other day, until the total calculated required amount is given.

Iron Deficiency Anemia of Infancy: IMFERON provides a convenient safe means for restoring hemoglobin levels and iron reserves in anemic infants. Excellent results were obtained by Gaisford and Jennison[2] with IMFERON in 100 iron-deficient infants. From a pretreatment average of 54.5 per cent, hemoglobin levels rose to 87 per cent 10 weeks after the start of therapy. Clinical improvement paralleled this response. Premature infants and surgical cases were similarly benefited. IMFERON gave "...all the advantages of transfusion or intravenous therapy without the disadvantages."[2] There were no side effects in any of the infants treated. Wallerstein[3] confirmed these results, furnishing evidence that IMFERON is well absorbed and appears in the bone marrow 12 to 24 hours after injection. Results are equal to those with intravenous saccharated iron oxide without the unpleasant side effects. Sturgeon[4] showed that the first year's iron requirements in infancy can be supplied with three injections of IMFERON.

Iron Deficiency Anemia of Pregnancy: Nausea precludes oral iron therapy in many anemic pregnant women. In those with severe anemia who are first seen late in pregnancy, prompt hemoglobin regeneration is unobtainable with oral iron. IMFERON produced prompt hemoglobin responses in anemia of pregnancy,[5,6] the results being similar to those obtained with intravenous saccharated iron oxide. Side effects were virtually absent with IMFERON.[5,6]

Resistant Hypochromic Anemia: Patients who do not respond to oral iron, those who cannot take oral iron and those with gastrointestinal pathology respond well to injections of IMFERON.[7-11] While oral iron is of little value in treating the anemia of rheumatoid arthritis, IMFERON is "...as beneficial as intravenous iron and easier to administer."[8]

Present Studies: Published reports and recent findings of clinical investigators confirm the effectiveness and safety of IMFERON for hemoglobin regeneration and creation of iron stores. More than 70 studies are now being completed in the United States. Reports stress prompt hemoglobin response, ease of administration and freedom from side effects. Clinicians desiring additional information should request Brochure No. NDA 17, IMFERON, Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin.

References: (1) Brown, E. B., and Moore, C. V., in Tocantins, L. M.: Progress in Hematology, New York, Grune & Stratton, Inc., 1956, vol. I, p. 25. (2) Gaisford, W., and Jennison, R. F.: Brit. M. J. 2:700 (Sept. 17) 1955. (3) Wallerstein, R. O.: J. Pediat. *49*:173, 1956. (4) Sturgeon, P.: Pediatrics *18*:267, 1956. (5) Jennison, R. F., and Ellis, H. R.: Lancet 2:1245 (Dec. 18) 1954. (6) Scott, J. M., and Govan, A. D. T.: Brit. M. J. *2*:1257 (Nov. 27) 1954. (7) Grunberg, A., and Blair, J. L.: A.M.A. Arch. Int. Med. *96*:731, 1955. (8) Millard, J. B., and Barber, H. S.: Ann. Rheumat. Dis. *15*:51, 1956. (9) Baird, I. M., and Podmore, D. A.: Lancet 2:942 (Nov. 6) 1954. (10) Cappell, D. F.; Hutchinson, H. E.; Hendry, E. B., and Conway, H.: Brit. M. J. 2:1255 (Nov. 27) 1954. (11) Stevens, A. R.: A.M.A. Arch. Int. Med. *96*:550, 1956.

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receive adequate instructions about the nature of the disease and measures to be followed to prevent and detect complications. Thus, proper control necessitates frequent tests for glycosuria and ketonuria as well as rigid adherence to instructions relative to body weight, exercise, personal hygiene, and avoidance of infections. The patient should be under close medical supervision, and the physician should be notified immediately if any untoward reaction or complications occur. Since insulin is indispensable in the management of complications, all patients receiving tolbutamide should also be instructed in the proper use of insulin. Recognition of the symptoms and the measures to counteract impending hypoglycemia are likewise essential parts of patient education. In view of the ease with which oral medication is taken and the resulting possibility of a careless attitude on the part of the patient, dietary restrictions should be stressed even more firmly for patients receiving tolbutamide than for those taking insulin. In short, all of the usual diagnostic and therapeutic measures necessary to insure optimal control of the diabetic state with insulin are equally necessary for control with tolbutamide.

On the basis of both laboratory tests and clinical experience, the toxicity of tolbutamide appears to be low. Except for alterations in hepatic function tests in the dog, long-term and short-term toxicity studies in laboratory animals have not revealed any serious deleterious effects. Although indications of impaired liver function have been rare in humans, there is some evidence that tolbutamide may act, in part, by interfering with enzyme systems in the liver. Therefore, the drug should not be given to patients with liver damage. In the large-scale clinical trials to date, the over-all incidence of reported side-effects is about 3%. The most serious of these has been hypoglycemia, which is most likely to occur during the transition period. Other untoward reactions to the drug so far reported include gastrointentinal upsets, weakness, paresthesia, tinnitus, headache, and alcohol intolerance. Animal studies suggest that tolbutamide may prolong the action of barbiturates. For this reason, caution should be employed when administering barbiturate anesthesia to patients on tolbutamide therapy. As with other sulfonamide drugs, tolbutamide can produce such allergic skin manifestations as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions. If these occur, use of the drug should be discontinued and insulin therapy resumed on the previous dosage schedule. A mild type of leukopenia has also been observed. Although this potentially serious adverse reaction has been reversible, physicians should be alert to its possible occurrence. Patients should be warned to report to their physician immediately for leukocyte and differential counts in the event of fever, sore throat, and similar complaints. In contrast to the bacteriostatic sulfonamide drugs, tolbutamide has not caused hematuria, crystalluria, or other signs of renal damage. Thus, alkalinization of the urine or a large fluid intake is not necessary when this agent is employed.

Tolbutamide is a new drug and represents an entirely new therapeutic approach to the management of diabetes mellitus. Although clinical trials have been promising, much remains to be learned as to its ultimate usefulness and safety. This can only be attained through longer experience. As the drug comes into more general use, it is expected that the chief hazard will be a high incidence of ketosis during the transfer from insulin, chiefly because certain patients are not suitable candidates for such conversion. It should always be borne in mind that the only real advantage of tolbutamide over insulin is its effectiveness when given orally and that insulin remains the indispensable drug of necessity in all diabetic complications. When properly employed, tolbutamide can provide increased comfort, well-being, and convenience for a selected segment of the diabetic population. Improper or careless use, by physician and patient alike, will result in therapeutic failure or serious consequences.

Dosage

If preliminary objective and subjective observations indicate patient eligibility for tolbutamide, therapeutic trial is initiated by the oral administration of 3.0 Gm. on the first day and 2.0 Gm. on the second day. This initial dosage applies to all diabetics, whether or not they are receiving insulin. After the second day of therapy, dosage is gradually reduced, until a minimum requirement adequate for satisfactory control of blood sugar and glycosuria has been established. Trial of the drug should not exceed one week. In responsive patients, the maintenance dose may vary between 0.5 to 1.5 Gm. per day but should not exceed 2.0 Gm. The drug may be taken as a single dose each morning or in divided doses after meals, the latter schedule being preferable from the standpoint of gastric tolerance.

In converting diabetic patients from insulin to tolbutamide therapy, the insulin therapy should not be stopped abruptly. During the withdrawal period, the urine should be tested as frequently as three times daily for sugar and ketone bodies and the fasting blood sugar level determined before and four hours after the first dose. In patients with insulin requirements of less than 40 units per day, tolbutamide therapy may be initiated with a concurrent 30 to 50% reduction in insulin dosage. Depending on responsiveness of the patient, the insulin dosage is then reduced in a daily stepwise manner until complete conversion has been achieved. Trial of the drug in patients requiring more than 40 units of insulin per day is best accomplished in a hospital. In these patients, insulin dosage is reduced only 20% on the first day of tolbutamide therapy, with further careful reduction if adequate response is observed. Too rapid conversion may result in aggravation of the diabetic state, even in patients with a small insulin requirement.

Since most complications with tolbutamide occur during the conversion period, it is imperative that diabetic patients be under close medical supervision at this time. Regardless of the severity of the disease or prior treatment, all patients should be seen daily for the first week of therapy. During the first month, physical examinations and blood sugar level determinations should be carried out on a weekly basis. If sore throat, fever, or even malaise appears, a leukocyte count is indicated immediately. Thereafter, the patient should be checked at least once a month.

Applicable commercial name: Orinase.

The Upjohn Company cooperated by furnishing scientific data to aid in the evaluation of tolbutamide.

J. Am. Med. Assoc. **164:1333 (July 20) 1957.**

Preparations

Tablets Tolbutamide (Orinase) 0.5 Gm., scored.

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*Data to be published by government hospital.

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Report of the Council

The Council has authorized publication of the following reports. Nonproprietary terminology is used for all drugs that are mentioned; when such terminology is not considered to be generally well known, its initial appearance is supplemented by parenthetic insertion of names known to be applied to commercial preparations.

H. D. KAUTZ, M.D., *Secretary*

Doses of Water-Soluble Vitamin K Analogues

In Hemorrhagic Disease of the Newborn

During the last year several papers have appeared indicating a relationship between high dosages of water-soluble forms of vitamin K administered intraperitoneally in the newborn infant and the occurrence of hemolytic anemia, hyperbilirubinemia, and kernicterus. In March, 1955, Allison[1] reported on a series of cases of kernicterus and hemolytic anemia in premature infants whose only treatment had been with relatively high doses of a water-soluble vitamin K analogue. He stated that, despite clinical experience, which has shown that a dose of 5 mg. per day of such a compound is adequate for treating hemorrhagic disease of the newborn, there is a widespread tendency to use much larger doses in the belief that this vitamin is innocuous under all circumstances.

A brief comment was later published by Laurance.[2] In his clinic the routine care of infants was modified by increasing the dosage of a water-soluble vitamin K analogue from 10 mg. once on admission to 10 mg. three times daily for three days. Shortly after this change he observed that six infants had developed clinical signs of kernicterus and subsequently died when they were from 6 to 13 days old.

Animal studies reported by Moore and Sharman[3] demonstrated the effect of intramuscular injections of the water-soluble analogues of the vitamin in producing hemoglobinuria in rats deficient in vitamin E. Neither an aqueous preparation of vitamin K_1 administered intraperitoneally nor orally ingested, water-soluble analogues caused hemolysis in these experimental animals.

Recently Meyer and Angus[4] studied the effect of a a water-soluble analogue of Vitamin K which increased serum levels of bilirubin in infants during the first week of life. Most severe bilirubinemia occurred in the premature infants. It was concluded by these authors that, rather than effecting hemolysis, the action of the vitamin might be hepatotoxic; however, there is no conclusive evidence to prove this. The authors pointed to the risk of development of kernicterus in premature babies when the serum bilirubin is increased above 18 mg. per 100 cc. of serum.

This effect of vitamin K dosage on plasma bilirubin in premature infants was also studied by Bound and Telfer.[5] Their findings indicated that a decrease in the instance of kernicterus of prematurity could be anticipated if the practice of giving large doses of vitamin K analogues were abandoned.

Letters of warning by Severinghaus[6] appeared in several pediatric journals calling attention to the harmful effects described. It is important to emphasize more generally the danger of high doses of the water-soluble vitamin K analogues administered to infants. There is ample evidence that a single dose of a water-soluble analogue equivalent to 1 mg. of synthetic vitamin K (menadione) is adequate to prevent hemorrhagic disease in the newborn. This would correspond to a dose of 3 mg. of menadiol sodium diphosphate (Synkayvite Sodium Diphosphate, Vitamin K Analogue). Therefore, since this vitamin can cause serious metabolic changes under the conditions described, it is unwise to exceed this dose level.

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J. Am. Med. Assoc. 164:1331 (July 20) 1957.

Report to the Council

The Council has authorized publication of the following report. Nonproprietary terminology is used for all drugs that are mentioned; when such terminology is not considered to be generally well known, its initial appearance is supplemented by parenthetic insertion of names known to be applied to commercial preparations.

H. D. KAUTZ, M.D., *Secretary*

Rheumatoid Arthritis

Current Status of Treatment

W. PAUL HOLBROOK, M.D., DONALD F. HILL, M.D. and CHARLES A. L. STEPHENS JR., M.D., Tucson, Ariz.

Rheumatoid arthritis is a disease involving many connective tissues of the body and manifesting itself as a profound systemic disturbance. Inflammation of the joints and a chronic progressive crippling polyarthritis are only the most obvious manifestations of this process. For many years therapeutic procedures have been based on etiological theories: foci of infection, deranged carbohydrate metabolism, intestinal toxemia, endocrine imbalance, hypersensitivity to various antigens, neuropsychiatric factors, and many others. Treatment directed along etiological theories has so far failed, and we must admit that, as yet, we have discovered no specific etiological agent and no single specific cure. The recent increase in basic research in biochemistry, histochemistry, immunology, and biophysics gives new hope that the pathogenesis of this disease may soon be uncovered.

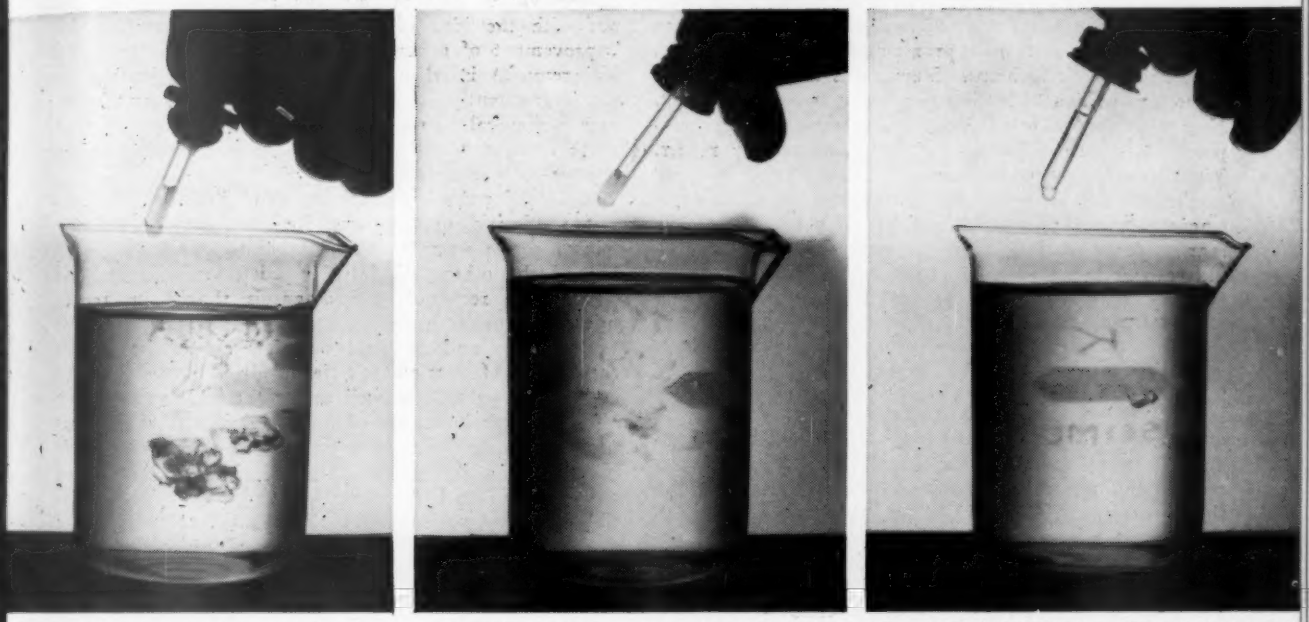
From the Southwestern Clinic and Research Institute.

Temporary Improvement

Many agencies produce temporary improvement in the disease. Artificial fever, anesthetics, starvation, and emotional crises will occasionally be followed by definite improvement; transfusions are, in some instances, followed by a partial remission; pregnancy and nonhemoyltic jaundice of sufficient degree produce remissions. In rheumatoid arthritis the immediate and dramatic effects are well known of corticotropin

The first "Predni-Steroid" —in true solution[3]

more soluble than Hydrocortisone[1] or Prednisolone[2]



1. The solubility of hydrocortisone acetate in water is 0.01 mg./cc. Note cloudy white suspension of insoluble steroid.

2. The solubility of prednisolone acetate in water is 0.01 mg./cc. Suspended particles of steroid (as shown in #1 and #2) are irritating.

3. The solubility of 'HYDELTRASOL' (prednisolone 21-phosphate as the monosodium salt) in water is 580 mg./cc. No undissolved steroid apparent

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CLINICAL COMMENTS: "It is felt that prednisolone is the most valuable steroid for topical use." Turner, L., *Am. J. Ophth.* 43:30, Jan. 1957. "The qualities of prednisolone phosphate appear more desirable . . . than those of all previous preparations." " . . . the phosphate form has prevented the local irritating effect caused by the large clumping particles, has been more acceptable to the patients and has been clinically effective." Lippmann, O., *A.M.A. Arch. Ophth.* 57:339, March 1957.

PRODUCT FACTS

DESCRIPTION: In 'HYDELTRASOL' Merck Sharp & Dohme presents the first family of truly soluble "predni-steroids." Each product contains a unique new steroid ester—prednisolone 21-phosphate alone or in combination with neomycin sulfate.

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(Acthar, Corticotropin, Depo-Acth) and the glucocorticoids, including cortisone (Cortisone, Cortogen, Cortone) acetate; hydrocortisone (Cortef, Cortril, Hycortole, Hydrocortone); prednisolone (Delta Cortef, Hydeltra, Meticortelone), and prednisone (Deltasone, Deltra, Meticorten). Approximately 90% of patients respond well and usually immediately to these substances. Phenylbutazone (Butazolidin) may produce initial improvement in approximately 40% of patients with rheumatoid arthritis. Remissions also occur spontaneously without identification of a remission agent. Nearly all of these periods of improvement are temporary, and sooner or later the disease activity recurs. We do not entirely understand the mechanism of these remissions, but the very fact that the disease in its early stages is reversible should add not only impetus to the search for the basic mechanism but confidence in ultimate success.

Long-term Basic Program

Inasmuch as rheumatoid arthritis is a chronic disease and usually a lifetime problem, emphasis should be placed on long-term treatment. Despite the lack of a specific cure, physicians can, with the present knowledge, prevent most of the deformities and sufficiently modify the disease to restore a majority of these patients to useful lives. Under inadequate treatment, patients with rheumatoid arthritis will continue to develop progessive crippling deformities and joint destruction. When a specific cure is discovered, it will not correct deformities or restore joints already destroyed. It is therefore essential, in the long-term management of this disease, to place every patient on a basic program directed toward the individual as well as his disease. Such a basic program should include at least the following eight items: psychological adjustment, a balance between rest and activity, diet and bowel management, correction of anemia, cautious removal of foci, relief of pain, corrective and postural exercises, and prevention and correction of deformity.

Psychological adjustment is essential for every patient. He must be told quite frankly what is known and what is not known about his disease. Failure to properly orient a patient to the long-term problems of rheumatoid arthritis is largely responsible for the fact that there are thousands who seek quick cures and quack remedies. Adjustments to family, business, and economic factors are essential. The patient must be taught to think in terms of months and years, not weeks. A very fine balance between knowledge of the facts and hope for the future needs to be achieved. No treatment of this disease will be successful over a prolonged period without this preparation.

Rest and activity should be carefully balanced on the basis of fatigability and pain. Moderate activity is helpful, provided the patient is not attempting to walk on bent and painful joints and provided the activity is followed by adequate rest.

Diet and bowel management must be prescribed accurately by the physician. This is essential, not because there are special diets that will cure arthritis but because the physician must make certain that the patient is on a highly nutritious, well-balanced diet; unless one is prescribed for him, he will most certainly, sooner or later, embark on one of the fad diets.

Correction of anemia in rheumatoid arthritis is often difficult, and simple iron preparations usually fail to help. A trial of one of the iron preparations is sometimes effective, though gastric irritation is often a problem. It is doubtful that liver, cyanocobalamin (Vitamin B_{12}), or other injections materially alter the anemia. When the disease is early and acute, three or four small fresh blood transfusions given at weekly intervals not only may help correct the anemia but often will give temporary improvement in the arthritis.

Removal of foci of infection should be undertaken not with the idea of curing the disease but only for improvement of general health. It is well to approach foci removal in rheumatoid arthritis with caution, as not infrequently an acute exacerbation may follow such a removal. Prophylactic antibiotic therapy and, in acute cases, a blood transfusion are worth doing before removal of a definite focus.

Relief of pain is usually accomplished by adequate rest; splinting or supports for the acutely affected joints; gentle warmth, but not baking; and aspirin or one of the other salicylates in adequate amounts. If opiates are required, the diagnosis should be reconsidered.

Corrective and postural exercises should be taught carefully and carried out faithfully, because for the ambulatory patient, as well as for the bed patient, they offer the best insurance of maintaining motion and improving muscle tone, thus preserving joint and muscle function.

Prevention and correction of deformities are essential in every patient with rheumatoid arthritis. The probability of flexion contraction and residual deformity should be anticipated and prevented. Much has been written on this subject, and every physician who accepts responsibility for treating even one patient with rheumatoid arthritis must be alert to this aspect of the management of this problem. Deformities can now be largely prevented and very many corrected after they occur. Knee flexion contractions in patients who now fill the wheelchairs can be prevented 100%. Prevention of deformities is simple and easily accomplished. Their correction is much more difficult and time-consuming.

Elective Measures

Once the patient is established on a full basic program, the physician is then free to choose from among the several elective procedures or measures, such as transfusions; administration of gold salts; change of climate; x-ray therapy; pregnancy, administration of gluco-corticoids, including cortisone, hydrocortisone, prednisolone, and prednisone; and administration of corticotropin (ACTH), phenylbutazone, and experimental anti-inflammatory agents.

Transfusions. Patients with acute early rheumatoid arthritis often respond well and occasionally dramatically to repeated transfusions of ordinary fresh blood. Usually 250 to 300 cc. given weekly for three to five weeks is the method of choice. Transfusions are not advised for the management of the chronic stage of the disease.

Gold Therapy. Despite more than 25 years of experience with gold salts in the treatment of rheumatoid arthritis, some differences of opinion still remain among students of the disease as to the value of gold therapy. We believe that gold is still the elective agent of choice in properly selected cases. In early active peripheral rheumatoid arthritis with minimal joint destruction and in the palindromic phase of rheumatoid arthritis, it offers the best chance of a very long and satisfactory remission. We regard palindromic rheumatism as an atypical rheumatoid arthritis. Gold

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therapy is seldom worth using in the far-advanced disease with much joint destruction and very little inflammatory reaction remaining. Although toxic effects may occur, we believe that with adequate precautions they are less frequent and less serious than those encountered in long-term therapy with gluco-corticoids. Should toxic manifestations occur with gold therapy, corticotropin appears to be a specific for the skin manifestations and of value in other toxic effects. It is far easier and safer to use than dimercaprol (BAL), one of the helpful antidotes for gold toxicity. If the disease is acute, we frequently use minute doses of purified corticotropin (10 units of the gel given subcutaneously) three times weekly during the first few months of gold therapy and have no difficulty discontinuing its use when the gold remission occurs. Some temporary relief persists from this minute amount for 12 to 24 hours. When gold is used properly in selected early cases, effective remissions are secured by this routine in a very worthwhile percentage of cases. Another point to be borne in mind is that once a remission has occurred, usually after three to five months, gold therapy is not discontinued, but maintenance dosages are administered at longer intervals for years.

Climate. A small percentage of patients with rheumatoid arthritis experience definite improvement with a change to a dry, warm climate. The chance that climate may help does not warrant disruption of a family's economic security, as climate is no panacea for rheumatism and certainly not a cure for rheumatoid arthritis. Climate is also no substitute for careful medical supervision. Most patients with rheumatoid arthritis are more comfortable and more easily cared for in a suitable climate, but a minimum of three to six months is required for a trial.

X-ray Therapy. Therapy with x-ray is not helpful in peripheral rheumatoid arthritis, but it is one of the valuable aids in rheumatoid spondylitis.

Pregnancy. In a very high percentage of patients with rheumatoid arthritis, pregnancy results in excellent remissions. However, the remission lasts only for the term of the pregnancy.

Gluco-corticoids (Corticosteroids). It is now generally agreed that the effects of the gluco-corticoids are only suppressive and do not alter the underlying disease mechanism. Moreover, joint destruction may continue to advance even during excellent clinical remissions. Neither intermittent courses of treatment with these substances nor continuous administration of effective suppressive doses has resulted in very encouraging results in long-term therapy. In our four-year control study of 36 patients with early active rheumatoid arthritis who were treated with maximum safe suppressive doses of cortisone, 33 patients achieved a grade 1 or grade 2 remission initially. After two years only two patients maintained this degree of improvement, and at the end of four years no patient remained in grade 1 or grade 2. Only two patients were receiving enough benefit to remain on therapy with the medicaments after four years. In a group of 60 patients with less active disease and advanced joint changes who were selected primarily for rehabilitation, the results of minimal doses of cortisone appeared to be very worthwhile. Cortisone acetate was administered orally in doses of 50 mg. per day or less, with no attempt at suppressing the disease, but only in an attempt to assist rehabilitation. Of these 60 patients, 26, or nearly half, were still being materially helped at the end of four years.

Hydrocortisone is a more potent anti-inflammatory agent than is cortisone, but the unfavorable physiological effects are qualitatively the same. In the systemic treatment of rheumatoid arthritis, its advantages over cortisone are not impressive. Hydrocortisone acetate, employed as a local anti-inflammatory agent, is given to selected patients by intra-articular injection, with definite help.

Prednisone and prednisolone, even more powerful anti-inflammatory agents, do not significantly disturb electrolyte and water balance as do cortisone and hydrocortisone. However, in our experience, long-term therapy with these drugs is no more successful than with cortisone. These substances produce marked adrenal suppression, frequently lasting for several weeks after withdrawal of the drug. The risk of peptic ulcer (often silent with perforation), disturbed glucose metabolism, and the tendency to capillary bleeding are increased with administration of these substances as compared to cortisone. Minimal doses of 5 to 7.5 mg. daily of prednisone and prednisolone are often very helpful in rehabilitation, though even with this dosage unfavorable physiological effects may occur.

When one considers the frequency of unfavorable physiological effects associated with long-term gluco-corticoid therapy, together with the high failure rate experienced, it should be clear that only after careful selection of patients and for special reasons should the gluco-corticoids be used in early active rheumatoid arthritis. Although our experience with juvenile rheumatoid arthritis is not extensive, it appears that children tolerate long-term gluco-corticoid therapy better than do adults. A number of reports by other investigators express a similar opinion.

Corticotropin. The results of our four-year study in which continuous suppressive doses of corticotropin were given for the treatment of rheumatoid arthritis are quite similar to those achieved with cortisone and show the same high failure rate. Corticotropin is of value is restoring adrenal function when suppression has occurred with the use of gluco-corticoids, especially when discontinuance of their use becomes necessary.

Phenylbutazone. The initial response of patients with peripheral rheumatoid arthritis to phenylbutazone is not as dramatic as that to the gluco-corticoids or corticotropin, nor does as favorable a response occur in so high a percentage of patients. In our experience approximately 40% of the patients with peripheral rheumatoid arthritis achieve an initial worthwhile improvement, but a relatively small number of these reach a grade 1 or grade 2 remission. However, once patients attain a worthwhile improvement without significant toxic effects, the failure rate is not so rapid as with gluco-corticoids and corticotropin therapy. Adverse physiological effects occur and require constant vigilance. These may include edema, hypertension, rashes, symptoms of peptic ulcer, and lowered hemoglobin levels. Blood dyscrasias and hepatitis have also been reported. Daily dosage in excess of 0.4 Gm. is not likely to be more effective than smaller doses, and the risk increases with the larger doses. In peripheral rheumatoid arthritis, phenylbutazone is best reserved for the occasional case which does not respond to other measures and which does show a favorable response within 10 days to relatively small doses. Most toxic manifestations, although not all, occur during the first three months of treatment. Despite the limitations of phenylbutazone in the treatment of peripheral rheumatoid arthritis, it is an extremely useful and effective

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agent in rheumatoid spondylitis. Our studies show that 89% of patients with rheumatoid spondylitis, without peripheral involvement, responded rather dramatically to initial administration of no more than 0.2 Gm. of phenylbutazone daily. Forty-eight such patients who responded well initially, without toxic effects, have now been followed for more than four years. Of this group, 44 are still doing remarkably well. Of the four patients removed from treatment, one developed a bleeding peptic ulcer and one hematuria with recurrent urinary calculi; the drug was no longer effective in two of the patients. This represents an extremely low failure rate. We have withheld x-ray therapy from the patients with rheumatoid spondylitis who are doing well on this routine because the results, so far, are superior to those achieved with x-ray therapy.

Other Experimental Anti-inflammatory Agents. Several new synthetic gluco-corticoids are now being investigated, and it is certainly possible to increase several fold the anti-inflammatory effects by altering the structure of the molecule. The problem is to achieve this without also multiplying some of the undesirable physiological effects that occur. Inasmuch as prolonged treatment is essential to the management of this disease, evaluation of these newer steroids from the long-term viewpoint is obviously impossible at this time. Search for a synthetic steroid with only anti-inflammatory action is being continued, but at this writing such a compound which is entirely free of undesirable physiological side-effects has not been reported. Postpartum and placental serum, primaquine phosphate, quinacrine (Atabrine) hydrochloride, chloroquine (Aralen) phosphate, nitrogen mustards aminopterin sodium, procaine hydrochloride given intravenously, para-aminobenzoic acid, adenosine triphosphate, heparin sodium, and others previously have been reported to show favorable therapeutic effects in rheumatoid arthritis. However, they have been largely abandoned for this purpose either because of excessive toxicity or failure to maintain what appeared to be early improvement. In several very recent reports chloroquine has again been described as a useful drug.

Comment

The present trend in treatment of rheumatoid arthritis is to emphasize a complete and carefully planned basic program, which should embrace at least the eight fundamental items discussed previously. Aspirin, or one of the other salicylates, is considered to be the safest and most desirable of the drugs used for relief of pain. Of the elective procedures, gold therapy administered in early active disease, when successful, often induces long and quite satisfactory remissions. Gluco-corticoids, given in minimal doses, are extremely valuable in rehabilitation and in special situations in which the disease is older and much less active. Corticotropin may be used in the same fashion, with minimal doses given every other day. Small doses of phenylbutazone, administered under careful supervision, are effective in the control of rheumatoid spondylitis and show a low failure rate in this form of the disease.

In view of the rapid failure rate, the unfavorable physiological effects, and the progression of joint destruction, all of which are associated with long-term therapy, we believe that the gluco-corticoids have only a very limited place in the treatment of early active rheumatoid arthritis. Furthermore, the psychological impact of the early dramatic improvement followed by gradual failure and relapse as the months go by is indeed an emotional disaster for the patient and often a cause of referral by the physician. Some excellent studies have shown that the five-year results with cortisone are no better than those with aspirin. However, these statistics are not quite fair, because they do not take into account the total working days during the period. There are occasions when, with a full understanding between patient and physician, it is advisable or necessary to secure maximum physical activity over a given short period of time, and this can often be accomplished with the gluco-corticoids. It is essential that the cost to the future of buying this time must be carefully evaluated and understood by the patient as well as the physician. It is only fair to state that honest differences of opinion exist, regarding the role of gluco-corticoids in the treatment of rheumatoid arthritis. The conclusions expressed in this report, while shared by many, would be thought too pessimistic by some and too optimistic by others.

Finally, if the physician will spend sufficient time and effort to establish his patient on a sound basic program and only then, if necessary, select elective measures best suited to the individual problem, the results of treatment will be surprisingly rewarding.

J. Am. Med. Assoc. *164*:1469 (July 27) 1957.

Report to the Council

The Council has authorized publication of the following report. Nonproprietary terminology is used for all drugs that are mentioned; when such terminology is not considered to be generally well known, its initial appearance is supplemented by parenthetic insertion of names known to be applied to commercial preparations.

H. D. KAUTZ, M.D., *Secretary*

Congestive Heart Failure

Current Status of Therapy

CALVIN F. KAY, M.D., Philadelphia

The symptoms and physical signs of congestive failure are well known in clinical practice, and the common forms of therapy are widely and effectively used. In the past several years, a great deal has been learned about the hemodynamic and chemical disturbances associated with congestive failure. Generally this has been made possible by the wide application of advanced techniques for the measurement of cardiovascular dynamics (cardiac catheterization, indicator-dilution methods), for the investigation of hormonal chemistry and physiology, especially that of the adrenal gland, and for the study of body water and electrolytes. The many observations have been so variously interpreted that no uniform agreement exists upon even the general outline of the pathogenesis of congestive failure, and, for lack of information, many important details are either controversial or obscure.

Pathogenesis

Although congestive failure may be the ultimate result of a single anatomic lesion such as syphilitic aortic insufficiency and may be permanently abolished

From the Department of Medicine, School of Medicine, University of Pennsylvania, and the Robinette Foundation of the Hospital of the University of Pennsylvania.

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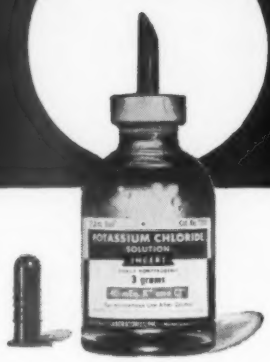

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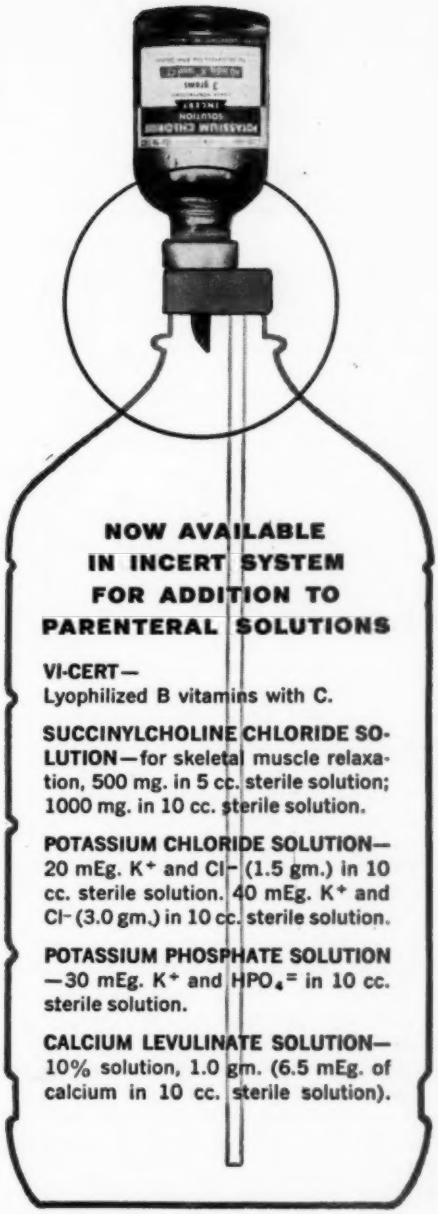

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by relief of a single anatomic defect such as closure of a patent ductus arteriosus, the development of failure is invariably complex. The site of congestion is determined, in part, by the relative functional incapacities of the two ventricles (left-sided and right-sided failure), For example, if a dog with hypertension is subjected to aortic insufficiency, pulmonary venous pressure rises as blood accumulates behind the functionally deficient left ventricle, and pulmonary edema occurs. If, in addition, an atrial septal defect is also present, left atrial pressure is relieved, systemic venous pressure rises, and generalized edema develops instead of pulmonary edema. Many comparable examples could be cited in human subjects. Besides influencing the site of congestion, this mechanism (backward failure) augments and perpetuates fluid retention but is probably of less importance in producing the retention than are a host of hormonal, chemical, reflex, nutritional, and vascular anatomic changes that result, directly or indirectly, from impairment of effective cardiac output (forward failure). In some manner these changes produce a renal retention of sodium and water, increase in blood volume, and alteration of the water and electrolyte content of the tissues.

Cardiac Output. Effective cardiac output may be impaired because it is actually deficient. Inadequate cardiac output usually results from impaired myocardial function, the basic defect responsible for most congestive failure. Sometimes the mass of muscle is inadequate, as after repeated myocardial infarction; sometimes the muscle is inflamed, as in rheumatic carditis, or degenerated, as in severe anemias. Usually, however, the muscle fibers have been subjected to progressive tension in diastole or excessive resistance to contraction. In time, this leads to stretching of muscle fiber and hypertrophy. Ultimately, for reasons that are now obscure, the capacity for contraction declines, despite an adequate supply of chemical energy. Although the potential contractile force may be normal, or at least adequate, it may be ineffective in providing sufficient circulation because of valvular incompetence, an excessive heart rate, or useless shunting of blood within the heart, great vessels, or lungs. Inadequate output may also result from mechanical obstruction within the heart (valvular stenosis) to the venous inflow (constrictive pericarditis) or to the ejection of blood from the ventricle (pulmonary embolism). With obstruction, myocardial contractile functions are ordinarily impaired either acutely (embolism) or progressively over a long period of time (systemic or pulmonic hypertension).

In other instances, congestive failure may develop in the presence of a heart that is anatomically and functionally normal or nearly so. Congestive failure then appears to result from maldistribution rather than from deficient total cardiac output. The kidneys may be deprived of an adequate blood supply either directly or reflexly. Various electrolyte excretion control mechanisms such as adrenal production of aldosterone are disturbed, while a normal or excessive total output is largely diverted elsewhere. The blood is dumped through low peripheral resistance pathways into the veins, forcing the heart to struggle under the distending load of massive venous return. This is the so-called high-output failure associated with thyrotoxicosis, anemia, infection, pulmonary disorders, arteriovenous aneurysm, or pregnancy. Unless unusually severe, these disorders rarely cause advanced congestive failure if the functional capacity of the heart is normal. When they are combined with intrinsic heart disease, otherwise compensated, congestive failure is promoted. During exertion the limited output of the diseased heart is diverted, especially into the dilated capillary beds of skeletal muscles, loading the venous return. The heart rate may be accelerated beyond the level of maximum efficiency, anoxia may develop, and the arterial pressure load may increase. These sequelae of exertion promote congestive failure in a manner analogous in many respects to that of the mechanisms responsible for high-output failure.

Fluid Retention. Congestive heart failure is, by definition, associated with retention of fluid. We are concerned not only with the quantity of the retention but also with the site of its accumulation. A small fluid accumulation in the lungs may demand more attention than a large one in a leg, and a clinically obscure intracellular overhydration may be of greater practical importance than an obvious ascites. The retention of water and sodium predominantly results from a disturbance of renal function as it is influenced by diminished renal blood flow, increased renal venous pressure, reflex nerve stimuli, and altered endocrine secretions. Retention is also promoted by the hydrostatic and membrane permeability effects of increased venous pressure, anoxia, lymphatic obstructions and hypoproteinemia. Some of the fluid retention is usually intravascular, although the magnitude of hypervolemia is considerably less than might be expected from observation of the distended veins. Most of the fluid accumulates in the interstitial tissue or in the body cavities. Alterations of intracellular fluid and electrolyte content are variable, difficult to measure, and uncertain in mechanism; however, in severe refractory edemas, intracellular overhydration, potassium deficiency, and total body sodium excess are frequently present.

Other Factors. A patient with congestive heart failure usually has obvious intrinsic heart disease that may reasonably be held responsible for the failure. The attending physician must consider the possibility that the heart lesion is amenable to surgical correction. He must not allow unrelated but important other diseases to go undiscovered and unattended, and he has an initial and continuing responsibility to recognize and treat disorders that aggravate and perpetuate the congestive failure. Of these, six are especially important: thyrotoxicosis, infection (especially subacute bacterial endocarditis), active rheumatic fever, thromboembolism, prostatism, and anemia. The clinical manifestations of any of these may be obscured by those of the intrinsic heart disease, but recognition and appropriate therapy may contribute outstanding success to the relief of the failure.

Preventive Measures

Congestive heart failure is best treated before it occurs. Preventive measures are essentially the same as treatment measures, applied with less vigor. It may test the talent of the physician to persuade the relatively asymptomatic patient to cooperate. In an acute problem such as myocardial infarction it is wiser to restrict salt from the beginning and to apply further appropriate measures at the first sign of fluid accumulation rather than to withhold treatment until the fulminant manifestations of failure have appeared. In chronic problems there is good reason to believe that failure begets failure; after failure, the heart may never regain the same functional capacity. A generation ago "prophylactic digitalization" was recommended for patients expected in the natural

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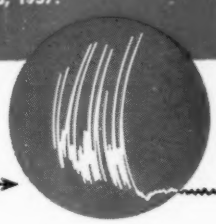

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course of events to progress into failure. The benefits of this policy, if any, have been difficult to assess, and the preventive use of digitalis is not widely accepted. It may be that a patient with progressive cardiac enlargement deserves digitalis therapy, but, whether digitalis is used or not, therapy should begin at the earliest sign of failure if not before.

Therapeutic Measures

A large number of drugs and procedures are effective in varying degrees in relieving congestive heart failure, more or less irrespective of the nature of the basic cardiac defect. The vigor with which these general measures are applied is governed by the severity of the disorder and the adequacy of response. A moderate restriction of activity may be all that is needed. If it is not, then digitalization or a moderate dietary restriction of salt may suffice. Diuretics may be helpful. In severe protracted congestive failure, the restoration of cardiac compensation may require all of these procedures and more.

Rest. Rest is of paramount importance to the patient with congestive failure, whether it is incipient or advanced. Physical activity should always be kept well below the restrictions demanded by symptoms, but restriction of physical activity is not synonymous with rest, which also means sleep and mental relaxation. Careful planning is essential to accomplish the most with the least exertion and to insure periods of daytime relaxation. Proper sleep may be promoted with the help of sedative drugs as needed.

Diet, Salt, and Water. In those patients who are in or predisposed to congestive failure, the kidney cannot or does not excrete as much sodium as that contained in the normal diet. Seven grams of retained sodium chloride (about 3 Gm. of sodium) withholds in the tissues more than 1 liter of water in order to maintain osmotic equilibrium. As the ingestion of sodium is decreased, excretion is reduced; however, a point is reached at which excretion exceeds ingestion. Water loss must accompany this sodium loss, or osmotic equilibrium may be and sometimes is disturbed.

Sodium restriction is consistently effective, not only in the prevention of peripheral edema but also in the management of pulmonary congestion, whether or not generalized edema is clinically apparent. These virtues have not been fully realized in clinical practice. Too often the diet recommended is so unpalatable that it is soon abandoned or disregarded to a point of uselessness; it unintentionally includes items of high-salt content, or it will not fulfill nutritional requirements.

The average, healthy individual usually ingests from 3 to 6 Gm. of sodium (8 to 15 Gm. of salt) daily. Many patients are greatly helped by a reduction to about 2 Gm. of sodium daily. This can be accomplished by avoiding the use of frankly salty foods and salt at the table. A further decrease to about 1 Gm. of sodium calls for a more restrictive food list and omission of salt from cooking. For patients with severe chronic congestive failure, it is necessary to reduce sodium intake to 0.5 Gm. or below. This demands rigid attention to dietary details and the addition of special, commercial dietary products to provide a sufficient variety to be acceptable to the patient.

A manual entitled "Food for Your Heart" is available to physicians on request from the American Heart Association. Physicans will find it instructive for themselves and highly satisfactory for the education of the patient. It contains specific directions for diets ranging from 0.5 to 3 Gm. of sodium, recipes for a variety of low-salt dishes and sauces, tables of salt content of most foods, and a list of especially prepared low-salt food products, including salt substitutes, and their manufacturers. A fuller discussion, with more complete dietary tables and tables of salt content of various municipal water supplies, is contained in the publication "Sodium Restriction Diets," available from the National Research Council, Division of Biology and Agriculture. It is of greater educational value to the physician but not quite so practical for most patients. As a supplement, a small pamphlet may be obtained from the Heart Association of Southeastern Pennsylvania. This pamphlet contains further recipes of interest to the low-salt gourmet together with lists of additional low-salt foods, commerical and otherwise.

For those not needing a restriction below 2 Gm. of sodium, a measured 1 Gm. of salt (the cap of a toothpaste tube is a convenient measure) placed each morning in a salt shaker will give the patient more satisfaction than double that amount added to the cooking. The liberal use of salt-free condiments is helpful, as are the salt substitutes, despite the frequent complaints of bitterness and after-taste. When renal impairment is severe, the potassium content of salt substitutes may contribute to the hazards of hyperkalemia.

Except for sodium intake, the diet is ordinarily unrestricted. In some patients, especially those with hyperlipemia and atherosclerotic disease, dietary restriction of fat may also be necessary. Most patients will select a diet containing adequate caloric, protein, and vitamin intake, but the physician must periodically make specific inquiry. It is pointless to restrict dietary salt intake and then to prescribe drugs containing sodium. Patients often use sodium bicarbonate or sodium salicylate without the knowledge or advice of the physician.

Since the total fluid intake is ordinarily not critical, the quantity may be governed by the patient's desires. Fluid intakes up to 6,000 cc. may hasten diuresis in those who have severe edema and who have not been on a salt restriction program. A forced high-fluid intake will not often help those whose conditions are progressively refractory to standard therapeutic measures and may promote water intoxication, especially in those with advanced intrinsic renal disease. Conversely, some patients will spontaneously restrict their fluids to 1,000 cc. daily or less. This is desirable as a temporary measure in previously untreated patients who may have recently ingested large amounts of salt and are already in hazardous condition (acute pulmonary edema). In chronic failure, intakes of 2,000 to 3,000 cc. daily are optimal, and most patients spontaneously place themselves in this range.

Digitalis and Digitalis-like Drugs

There is a growing tendency to use digitoxin (Crystodigin; Digitaline Nativelle; Digitoxin; Purodigin; Unidigin) and digoxin (Lanoxin) in place of digitalis for oral digitalization and maintenance. An old preparation, gitalin (amorphous) (Gitaligin), has been reintroduced into practice, and two new preparations, acetyl digitoxin (Acylanid) and acetyl strophanthidin, have been developed. Rapid intravenous digitalization, sometimes with unnecessary hazard to the patient, continues to be carried out with digoxin, lanatoside C, or ouabain.

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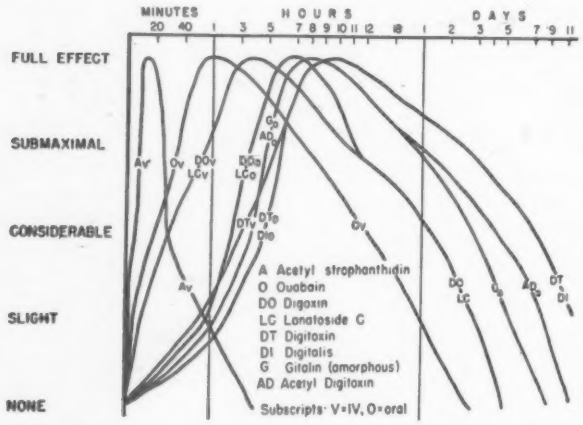
occasionally by slowing the ventricular rate but mainly by increasing the contractile force of the heart muscle. Belief has been revived in the possibility that a direct renal diuretic effect may also exist.

The qualitative biological effects of these preparations are very similar, and perhaps identical. Quantitative differences are obvious, especially in the percentage of drug absorbed from the gastrointestinal tract, in the rate of measurable onset and cumulation of biological effects, and in the duration of effects.

Strophanthus preparations are so poorly absorbed that they are not useful orally. Digitoxin is completely absorbed. Absorption of the other preparations ranges from about 67% for acetyl digitoxin to 10% for lanatoside C. Fortunately, absorption of any one preparation is reasonably uniform from individual to individual or in the same individual at different times. Hence, in clinical practice, a high percentage of absorption is not a great advantage, as is demonstrated by the excellent therapeutic record of whole leaf digitalis, of which only about 20% of the cardioactive priciples is absorbed.

The various preparations influence the heart at different rates of speed. Digitoxin is the slowest, acetyl strophanthidin is the most rapid, and the others range between the two. The degree of biological effect resulting from a single dose is plotted against time in the figure. The curves are rough approximations, since the responses of different individuals are not uniform. The terms on the ordinate are deliberately vague, because "level of digitalization" is clinically vague: a small dose of digitalis may reduce the ventricular rate in atrial fibrillation from 150 to 90, whereas a dose twice as large would reduce it from 150 to 80. The upward curves have several clinical connota-



Approximate curves of accumulation and decline of the biological effects of single doses of cardioactive preparations in man. (Adapted from *Circulation* 12:123 [July] 1955.)

tions, of which two are especially important. One pertains to the selection of a suitable drug. On the rare occasions when the safety of slower administration must be sacrificed to meet an urgent demand for rapid action, a preparation with a rapidly rising curve is indicated. The other pertains to the time interval between dosages. If further medication is given before the full effects of the preceding dose have accumulated, toxicity is invited. The decline curves vary even more from individual to individual than do the upward curves. A slow decline curve correlates with relatively small maintenance dosage requirements and with relatively long persistence of toxicity. The decline curves also provide some suggestion of the probable requirements for redigitalization when therapy has lapsed.

The prime indication for digitalis therapy is congestive heart failure resulting from defective myocardial contraction, from the inefficiency of excessive ventricular rate, or from a combination of the two. When congestive failure develops despite normal myocardial function, (cardiac tamponade), digitalis is usually useless and may be harmful. When the congestive failure results from a combination of mechanical factors (aortic stenosis) and of myocardial factors (the dilatation and/or hypertrophy that is the invariable result of functionally significant valvular disease), the effectiveness of digitalis is variable. Even when the fault lies entirely in the myocardium (acute rheumatic fever, diphtheritic myocarditis), digitalis may be of no value. However, when the heart is enlarged and congestive failure is present, digitalis will be beneficial as a rule.

Mention may be made of the use of digitalis preparations in certain disorders commonly associated with failure. In persistent complete heart block with failure, digitalis is indicated. It is not contraindicated but should be used with caution in incomplete or intermittent heart block or in patients with carotid sinus sensitivity. Angina pectoris is neither an indication nor a contraindication. After acute infarction, if all other appropriate measures have been used and evidence of congestive failure is nevertheless progressive, digitalis should be given before a state requiring rapid digitalization is reached; dosage approaching the toxic level should be avoided. In thyrotoxicosis, the results of digitalis therapy will often be disappointing until thyrotoxicity is controlled. When atrial fibrillation is present, no attempt should be made to reduce the ventricular rate below what would be expected in normal sinus rhythm. In patients with disturbed electrolyte balance, especially potassium depletion, toxic effects may occur from unusually small doses of digitalis. This is also a danger in the aged or debilitated.

Administration of a digitalis preparation is ordinarily a three-stage program. First, the physician seeks to establish a minimum effective level of digitalization within a reasonable time. In the patient of average size, who has not recently received digitalis and in whom no unusual sensitivity is predictable, the average oral initial digitalizing dose may be given in three or four divided doses during 24 hours (e. g., 0.4 mg. of digitoxin every 8 hours for three doses). (See the table.)

Second, an optimum level of digitalization is sought. This may be accomplished by somewhat more than average daily maintenance dosage. For example, 0.15 mg. of digitoxin may be given twice daily, with careful observation of the effects. In ambulatory patients in no urgent need for digitalization, the first and second stages may be combined by giving somewhat more than the average maintenance dose, 0.15 or 0.2 mg. of digitoxin daily; the effects should be observed over a period of several days or weeks.

The principal guide to optimum therapy is rarely clearly defined; it consists of clinical judgment based on the relief of the manifestations of congestive failure. In atrial fibrillation, digitalis is relatively ineffective in reducing the heart rate in the presence of

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[1]Slanetz, L.W.: J. Dent. Res. 31:35. 1952.

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thyrotoxicosis or fever. Otherwise the apical pulse rate is a useful index, provided the examiner is not misled by ectopic tachycardias (especially nodal paroxysmal tachycardia or paroxysmal atrial tachycardia with block; ventricular premature beats are usually recognized easily) actually induced by the digitalis at toxic levels, or by the labile reduction of apical rate resulting from the vagal stimulating action of the drug. Manifestations of toxicity may be obvious (nausea or vomiting, various arrhythmias) or obscure (anorexia, weakness, head pains, visual disturbances). They should be carefully watched for, and, when they occur, the point of maximum benefit has usually been reached or passed.

The third stage, prolonged maintenance, like initial and optimum digitalization, is an experiment in each individual. A reasonable estimate of dosage requirements is made; then, as events dictate, it is revised. When digitalis or digitoxin is used, several weeks may pass before an error in dosage in either direction becomes apparent. In most patients digitalis is helpful at doses well below the toxic range. Considered over a period of time, the slight benefits of higher dosage usually do not justify the discomforts and hazards that may ensue.

Digitalis and digitoxin are by far the most widely used preparations. They are the most slowly effective of the group. This is rarely a disadvantage, however, since in the vast majority of instances a few hours is not a significant delay. Their effects are also the most persistent. This is a distinct advantage insofar as it results in stability of the level of digitalization, once achieved. It is a disadvantage in that the toxic effects, once produced, last longer. Digitalis produces more local gastrointestinal irritation than does digitoxin when given in a large single oral dose; otherwise, manifestations of toxicity, cardiac and otherwise, are indistinguishable. Either of these preparations is highly satisfactory for most digitalization needs.

Some physicians prefer other preparations derived from digitalis, both for initial digitalization and for prolonged maintenance. The basis for such preference must rest principally upon proved differences in rates of accumulation and elimination among the various drugs. Variations in cost, stability, purity, uniformity, and percentage of absorption from the gastrointestinal tract are either small or of little consequence. There is a mass of convincing data to show that all digitalis preparations have approximately the same margin of safety between efficacy and toxicity. An exception to this generalization has been claimed for gitalin (amorphous). Some physicians have disagreed, though impressed by the value of administration of gitalin to several patients whose response to other preparations had been poor. From several reports of gitalin therapy, it is apparent that, when toxic effects occur, cardiotoxicity is often the first recognized manifestation; this is also the case when any other digitalis preparation is given. In our own studies we have attempted a controlled investigation of comparative toxicity and therapeutic effects, in which neither the patient nor the evaluating physician knew the drug or its dosage. The results have been extremely difficult to interpret on this objective basis; they revealed, however, no clear indication of relative superiority of digitoxin, digoxin, or gitalin (amorphous). The poor definition of the "level of digitalization" makes evaluation of the relative merits of digitalis preparations inexact. At this time there is no evidence that convincingly demonstrates a therapeutic-toxic ratio difference.

All the other preparations act faster than digitalis or digitoxin. Thus, it is claimed that, since the effects of each succeeding dose develop more rapidly, they are more clearly defined and more promptly usable in order to judge the next dose. It is also claimed that the danger line may be approached more safely because, if toxicity develops, it abates sooner. These claims have some merit, especially for the severely ill patient. In such a patient, one or two small extra doses of digoxin may be added to the regular schedule when it is suspected that further digitalization might be helpful. In the past, ouabain was recommended for this purpose, and recently the logic of the argument has been extended to administration of acetyl strophanthidin, a new rapid-acting intravenously given preparation that has a peak effect in about 10 minutes. Its effects quickly abate and are almost gone in one hour. A "digitalis tolerance test," using this drug, has been devised. Acetyl strophanthidin should be given only with full recognition of its potentially lethal hazard. Although the temptation to use it is not infrequent, it should be yielded to very rarely.

Acetyl digitoxin, gitalin (amorphous), and digoxin, progressively more rapid in action than digitoxin and digitalis, are also more labile. With digoxin, the decline in effect is such that two doses daily may be required to maintain stability of therapeutic level. Excellent and usually indistinguishable results can also be achieved by the proper use of digitalis, digitoxin, acetyl digitoxin, gitalin (amorphous), or digoxin for initial and maintenance digitalization.

*Approximate Doses of Various Cardioactive Preparations for Oral and Intravenous Use**

	For Initial Digitalization				For Daily Maintenance, Oral	
	Oral		Intravenous			
Preparation	Average	Range	Average, Mg.	Range, Mg.	Average	Range
Digitalis	1.2 Gm.	1-2 Gm.	...	...	0.15 Gm.	0.05-0.30 Gm.
Digitoxin	1.2 mg.	1-2 mg.	1.2	1-2	0.15 mg.	0.05-0.30 mg.
Acetyl digitoxin	2.0 mg.	1.5-2.5 mg.	1.5	1.3-2.0	0.3 mg.	0.1-0.6 mg.
Gitalin (amorphous)	5.0 mg.	4-8 mg.	...	...	0.5 mg.	0.25-1.0 mg.
Digoxin	3.0 mg.	1-4 mg.	1.0	0.8-1.6	0.5-0.75 mg.	0.25-1.0 mg.
Lanatoside C.	6.0 mg.	5-10 mg.	1.6	1.2-1.6	1.0 mg.	0.5-2.0 mg.
Ouabain	...	...	0.8	0.5-1.0	...	...
Acetyl strophanthidin	...	...	0.6†	?	...	...

* Adapted from Circulation 12:297 (Aug.) 1955.
† Maximum dose for a single injection, to be diluted and administered in not less than 5 min. The average total dose for full digitalization is approximately 1.2 mg.

The dangers of intravenous digitalization should be risked only if the situation is so critically urgent that the few hours needed for oral drug effects cannot be allowed to pass. In such emergency there will be little loss of effectiveness if only one-half of the digitalizing intravenous dose is given, for the half dose is usually sufficient to surmount the urgent phase, after which oral therapy may be instituted.

Toxic effects from digitalis occur oftener than in the past, chiefly because more patients are receiving digitalis in larger and more effective doses. Minor manifestations of toxicity are useful to a degree. Major manifestations are most frequently the result of excessive dosage, occasioned especially by inattention to warnings or by a failure to appreciate that the patient has already received a digitalis preparation. Since individual digitalis requirements deviate considerably and unpredictably

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from average requirements, the administration of average doses does not necessarily avoid toxic reactions or assure adequate therapy. Although intolerance is more frequently encountered in hypokalemia, it may also be present in the aged or debilitated and in patients with hypothyroidism or advanced hepatic or renal disease.

Toxic effects from digitalis are usually managed by withdrawing the drug, restricting the activity of the patient, and waiting. Even with digitalis and digitoxin, the most clinically stable of the preparations, definite improvement or complete relief is the rule within two or three days. If improvement is slower, hypokalemia may be suspected or digitalis toxicity may not really be the basis for the persisting symptoms.

Effective emergency treatment for the dangerous arrhythmias of digitalis toxicity has been developed. The patient should be attended constantly, and if possible, an electrocardiograph should be continously connected for intermittent recording. Oxygen, tourniquets, and levarterenol (Levophed) bitartrate should be available for immediate use if necessary. Unless there is reason to believe that hyperkalemia is present, potassium should be given orally as either chloride or citrate; a dose of 4 Gm. in cold fruit juice is administered, followed if necessary by 2 Gm. hourly for two hours. The intravenous route, however, is preferable. The standard intravenous preparation contains 3 Gm. (13 mEq. per gram) of potassium chloride in 20 cc. of water. This solution should be diluted to 500 cc. in 5% dextrose solution. It may then be given at a maximum rate of 5 cc. per minute until a total of 6 Gm. has been injected. The perfusion should stop if the arrhythmia is controlled. These rates of administration should be exceeded in the first six hours only in patients with frank potassium depletion. Additional potassium may be necessary later to prevent return of the arrhythmia.

In ventricular paroxysmal tachycardia caused by digitalis poisoning, procainamide is indicated if potassium is not available or if no effect has been achieved in three hours. A dose of 750 mg. of procainamide hydrochloride (three 250 mg. capsules) may be given orally, followed by 250 mg. hourly for three additional doses. If the patient is unable to take or retain oral medication, 50 mg. (0.5 cc. of a solution containing 100 mg. per cubic centimeter) may be given every two minutes in a suitable diluent for continuous intravenous drip until 300 mg. has been received. Then the rate is reduced to 50 mg. every four minutes until a maximum total of 1,000 mg. has been given. Electrocardiographic monitoring is absolutely necessary, and the blood pressure should be taken every minute. The infusion must be slowed if the pressure falls appreciably and stopped if it falls alarmingly. If the pressure does not rise promptly, levarterenol bitartrate should be given.

Recently there have been several preliminary reports of favorable results in major arrhythmias from the use of antimalarial drugs, chloroquine especially, and from the catechol amines, especially isoproterenol (Aludrine; Isuprel) hydrochloride. These drugs may ultimately be found useful in the management of major digitalis arrhythmias.

Diuretic Agents

Many agents are effective diuretics in normal, healthy individuals. Effectiveness declines as the need increases. When congestive failure is severe, the parenterally given mercurial diuretics are superior to all other diuretics. Preparations for subcutaneous injection such as meralluride (Mercuhydrin) sodium, mercaptomerin (Thiomerin) sodium, and merethoxylline (Dicurin) procaine are equally effective and generally less painful locally than the intramuscularly given preparations. Intravenous use is rarely advisable since toxicity is thereby much higher; occasional fatalities have occurred. The diuresis that follows a single injection of a mercurial diuretic may be enormous: 6,000 to 10,000 cc. or even more. This is distinctly undesirable. It is exhausting to the patient and may result in profound asthenia or even shock. In older men, previously asymptomatic, prostatic hypertrophy may cause acute urinary retention. Distressing leg cramps, which may occur with diuresis, are sometimes prevented by giving 0.5 Gm. of quinine sulfate with the mercurial injection. After a single or repeated large diuresis, toxic reactions from digitalis may develop. They are related to potassium depletion and not to mobilization of glycosides as was formerly believed. To avoid such massive diuresis, it is usually wise to start with a dose of 0.5 cc. of the appropriate solution of any of the drugs mentioned, increasing later injections to 1 or 2 cc. as results indicate. Morning injections are preferred because the peak diuresis usually occurs about 4 hours later and has largely subsided within 12 hours. Injections of 1 or 2 cc. each, given daily or on alternate days are probably most effective, with an occasional interruption to ascertain the need and effect of the drug. Weekly or twice weekly injections are often helpful to the home or ambulatory patient, sometimes compromising the disadvantages of massive diuresis with convenience and economy. Mercurial diuretics should not be used in the presence of acute renal disease such as acute glomerulonephritis, acute toxemia of pregnancy, or lower nephron syndrome, whether or not congestive failure is present.

Sensitivity to organic mercurial diuretics may be manifested by local induration and edema, by generalized urticaria, erythema, or rash, by fever, or by nausea and vomiting. These symptoms are not frequent and almost never occur with the initial injection. Rather they tend to augment in severity with each succeeding injection. The sensitivity may sometimes be avoided by changing the variety of mercurial. Unless a satisfactory diuresis (2,000 to 3,000 cc.) follows each injection, mercurial poisoning is likely to develop. Only a few injections are sufficient to cause it if the urinary output is below 800 cc. This complication is readily avoidable with proper attention. It is most often seen in patients who administer mercurials to themselves or those in hospitals in which a routine daily order continues unnoticed. When poisoning occurs, 1 cc. of a 10% solution of dimercaprol (BAL) in oil should be given intramuscularly every four hours for three days.

When congestive failure is severe, orally given diuretics are usually of little value except to potentiate the effects of mercurial diuretics, and even this influence is erratic and often disappointing. They are at times helpful to patients in whom digitalis and sodium restriction are not quite adequate to control fluid accumulation. When orally given diuretics are used, the frequency of need for mercurial diuretics is sometimes reduced, and/or sodium restriction may be slightly relaxed. These benefits are rarely impressive; even when they are, comparable benefits can usually be achieved by more careful attention to dietary salt intake.

Ammonium chloride may be given as enteric-coated

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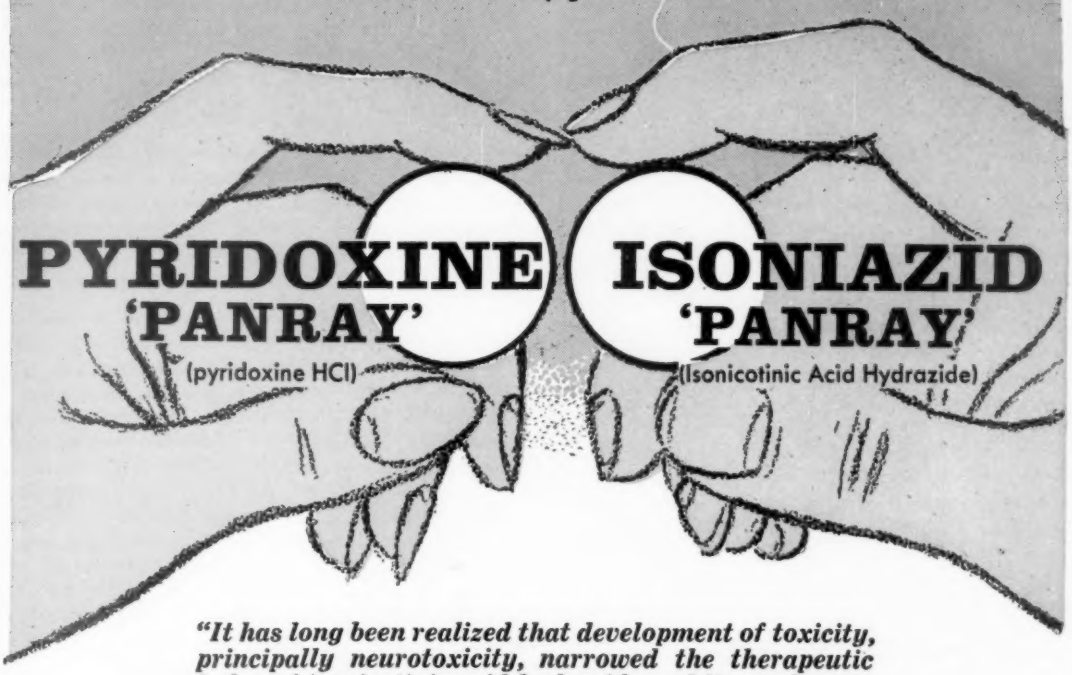

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[1]Sea View Bulletin 16:62 July '56 Tchertkoff, et al. JAMA 156:1549 (Dec. 25) 1954 Biehl & Viltner Am. Rev. TBc 70:266 Aug. '54 Hughes, et al. N. Eng. J. of Med. 255 #3 118-122, 1956 Carlson, et al.

tablets in divided daily doses of 4 to 6 Gm. for three days. If this therapy is immediately followed by use of a mercurial diuretic, the diuretic effects of the latter may be enhanced. The benefits of ammonium chloride may be balanced by the discomfort of the gastrointestinal symptoms, occasionally severe, produced in most patients. To be effective, the ammonium chloride should effect some degree of acidosis, which, in patients with impaired renal function or already existent acidosis, may rapidly become excessive and hazardous.

Acetazolamide (Diamox) is a sulfonamide carbonic anhydrase inhibitor that promotes bicarbonate excretion by the kidney, with consequent sodium loss. In severe failure, bicarbonate and potassium losses still occur, but sodium loss is much smaller, and diuresis is negligible. When failure is mild or moderate, 1 or 2 tablets (0.25 Gm. each) may be given orally on two or three successive mornings each week. A mercurial injection on the next day may result in a better diuresis than would have occurred without the adjuvant. Paradoxically, when acetazolamide is given simultaneously with the mercurial diuretic, diuresis is inhibited. Doses of 1 Gm. daily or more of acetazolamide will regularly produce drowsiness, paresthesias, and gastrointestinal symptoms. These symptoms are occasionally observed at the lower dosage levels previously suggested. Rare instances of dangerous toxic reactions have been reported. The efficacy of the drug is lost with continuous administration.

A dose of 0.5 Gm. of aminophylline diluted to 250 cc. in 5% dextrose solution, injected intravenously in 30 minutes, beginning three hours after the mercurial injection, may also be of some value in potentiating the diuretic effect. This and other xanthine preparations are not very effective as diuretics in either severe or mild congestive failure.

Preparations of exchange resins composed chiefly of cation exchangers, such as carbacrylamine resins (Carbo-Resin), increase fecal excretion of sodium (derived from either the food or the intestinal juices), and secondarily promote chloride acidosis and diuresis. In recommended doses of 8 to 16 Gm. three times daily, they may cause mild gastrointestinal discomfort and anal irritation. The latter may be controlled with psyllium hydrophilic mucilloid (Metamucil), available in the form of a powder containing 50% dextrose, which is administered in doses of 4 to 7 Gm. in water three times daily. The potassium depletion tendencies of the resins have been largely controlled by the addition of that ion to the preparations, and the acidifying effect is rarely significant. As with other diuretics, their effectiveness declines in proportion to the intractability of the failure. They are most useful in patients with mild or moderately severe congestive failure who cannot or will not sufficiently restrict their dietary intake of sodium.

Aminometradine (Mictine), a more recently introduced orally given diuretic, apparently acts by impairing renal tubular reabsorption of sodium. Its use has not been attended by major toxic effects, but not infrequently nausea, anorexia, and headache occur, especially if doses of 0.8 Gm. or more are administered daily. Dosages range from 0.2 to 0.8 Gm. per day given on alternate days or on three consecutive days each week. A closely related similar-acting drug, amisometradine (Rolicton), also has been introduced commercially.

It is generally recognized that effective diuretic doses of orally administered organic mercurial compounds regularly cause severe gastrointestinal disturbances. The diuretic versus diarrheic ratios have, however, improved with a succession of new organic mercurials. The most recent of these, chlormerodrin (Neohydrin), is undoubtedly an effective diuretic, well tolerated by some patients. It has been used especially in patients with mild failure who require 18.3 mg. (1 tablet) or less of the drug daily; however, even this dose may cause some anorexia, nausea, and diarrhea. When larger doses are required, the rising incidence of disturbing symptoms may sometimes be avoided by starting the patient on therapy with 1 tablet every other day, increasing to 1 or more daily if tolerated and if the urine output is satisfactory. This preparation must not be continued if oliguria persists. A suppository containing 0.5 mg. of mercaptomerin sodium has also been of some value in the management of mild or moderate degrees of failure.

Paracentesis

Free fluid in the pleural or abdominal cavities will often diminish or disappear coincidentally with the general relief of failure. If it contributes to an acute failure with dangerous or severely distressing manifestations, as in acute pulmonary edema, removal may be indicated as an emergency procedure. Otherwise, it is wise to await the success of other forms of treatment; if they do not succeed, the fluid may be tapped. Sometimes this results in a prompt diuresis. Too often the effusion promptly returns. Repeated paracentesis results in undesirable losses of protein and electrolytes.

Specific Problems

Thromboembolism. In some instances heart failure progresses in severity, despite the most skilled application of established therapeutic measures and a most diligent search for contributory disorders. Thromboembolism is a much more common contributory disorder than is generally appreciated. It not only contributes to the obstinacy of leg and thigh edema but also is responsible for multiple pulmonary embolization. Dramatic physical, roentgenographic or electrocardiographic manifestations of a single large embolization may be altogether absent, and those of each small embolization are obscured among the many subjective and objective abnormalities of the heart failure. Pulmonary embolization so commonly accompanies severe and protracted failure that anticoagulants are often advisable as prophylaxis. When leg edema is massive, with or without areas of inflammation and induration, when dyspnea becomes more and more distressing, and especially when icterus appears, anticoagulant therapy is almost always desirable.

Hyponatremia. Patients with intractable congestive heart failure often have depression of plasma sodium concentration. Hyponatremia is a laboratory sign and not a physiological diagnosis. It may result from plasma sodium depletion, relative to water, such as may be produced acutely by the rapid loss of fluids from the small intestine. Concomitant chloride reduction is almost always present, and the clinical manifestations are those of shock; tachycardia, falling blood pressure, and peripheral vasoconstriction. Conversely, hyponatremia may result from plasma sodium dilution, relative to water, such as may be produced acutely by the excessive parenteral administration of dextrose solution to an anuric patient. Confusion, restlessness, or even convulsions are among the manifestations. The hyponatremia so often found in a patient with intractable congestive failure after a protracted period of

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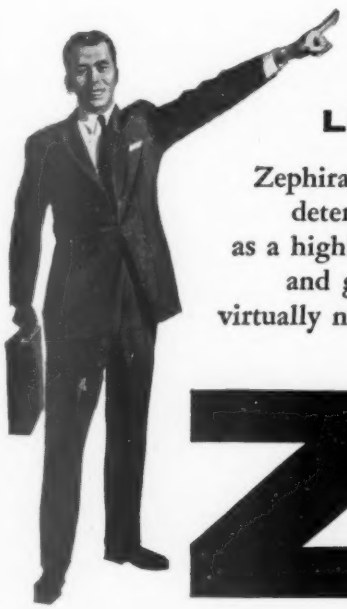

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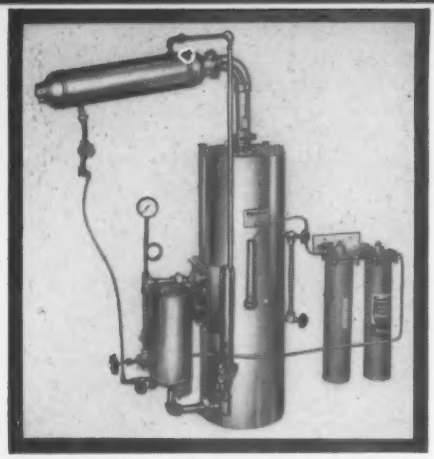

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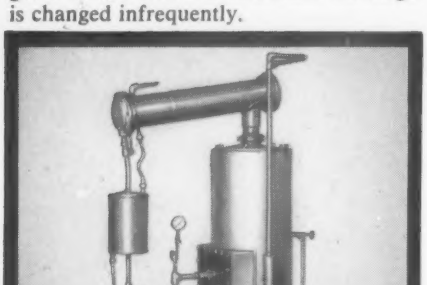

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therapy, especially when mercurial diuretics have been used vigorously, is usually a complex combination of plasma dilution and depletion in which the total body stores of sodium are often in excess of normal, while those of water are even more so.

The reasons for this hyponatremia are incompletely understood. It is probable that in these patients there is a new "set" to the control regulators for plasma water and sodium, and perhaps, for extracellular fluid volume as well. The control mechanisms (prominently including pituitary and adrenal secretory and thirst control) no longer strive to maintain the "normal" parameters.

It is fallacious to visualize hyponatremia as a direct, simple result of cellular uptake of osmotically active sodium, since there is nothing to suggest that cell walls become impermeable to water. Perhaps some sodium migrates into cells and becomes osmotically inactivated or segregated. Also, there is evidently some exchange of cellular potassium with plasma sodium as the cell loses its unique capacity for differentiating these two ions at the cell wall. The cellular hypoosmolarity may also be, in part, the result of cellular dilution. All of these factors could, and likely do, contribute to the plasma hyponatremia.

The therapeutic problem is always difficult and rarely brilliantly solved. Only a few choices are available. The first, and usually the best, is to ease up on diuretic therapy, search again and harder for factors that may be aggravating the failure, and avoid any direct attack upon the electrolyte disturbance. These procedures are particularly advisable when hyponatremia is found in a patient whose clinical state is satisfactory. The second choice is potassium therapy. If the potassium levels are low or at least not elevated, the cautious administration of 3 to 4 Gm. daily of potassium citrate or potassium chloride may sometimes produce diuresis and a rise in serum sodium levels. The third choice is alternating courses of ammonium chloride and a carbonic anhydrase inhibitor; this sometimes restores the ability of mercurials to induce diuresis, whereupon a rise in plasma sodium concentration may occur. The fourth alternative is administration of hypertonic salt solution, a procedure that has been subjected to much criticism. It is occasionally helpful in a patient with chronic failure whose condition has deteriorated clinically, with rising pulse and falling blood pressure, and in whom both sodium and chloride levels are excessively low. This procedure will fail unless the patient's fluid intake is restricted during therapy, despite the intense thirst usually experienced. A fifth choice, brief massive steroid therapy, has been recommended. I have had no personal experience with it, but I am not very favorably impressed by the reports of others.

Radioactive Iodine Therapy. Radioactive iodine therapy may be highly effective in the relief of congestive heart failure associated with thyrotoxicosis. In euthyroid patients with congestive failure, results are far less consistent and almost never impressive. Furthermore, certain manifestations of the induced hypothyroid state are distinctly undesirable. These patients are seldom happy. Their initiative and intellect may become too blunted for the limited sedentary pleasures of the cardiac, and those who must use their wits for economic survival may cease to be able to do so. When failure has been slowly progressive over a long time, despite carefully directed management and in the absence of thyroid toxicity, the physician may be encouraged to consider therapy with sodium radioiodide (I^{131}). It may be tried especially in the elderly, in the tense and restless individual who sleeps poorly, or in the presence of atrial fibrillation with a rapid ventricular rate that responds poorly to digitalis. Some patients in whom a measure of success is achieved may actually be thyrotoxic, even if the tests have not shown it.

Adrenal Surgery. Relief of congestive failure has been observed in a number of patients who have had adrenalectomy, with or without sympathectomy, for hypertension. In a series of 153 patients who had the combined operation, almost all of the 40 deaths resulted from stroke, myocardial infarction, or uremia, but none from congestive heart failure. This information, however, may prove to be of greater physiological significance in revealing the role of aldosterone in the mechanism of congestive failure than in suggesting a possible form of therapy for congestive failure.

Acute Pulmonary Edema. Acute pulmonary edema is a recurrent, distressing event in many patients. Most attacks follow exertion or awaken the patient from sleep. Occasionally this condition is precipitated by an acute arrhythmia. It is most common in those with chronic congestive failure but may appear in patients with little or no generalized edema, especially in those with hypertensive heart disease, aortic insufficiency, or a recent myocardial infarction. Most attacks subside spontaneously as the patient sits up and remains quiet. The general management of congestive failure will reduce the frequency and severity of such attacks.

If they persist, a suppository containing 0.5 Gm. of aminophylline or theophylline monoethanolamine (Theamin) given routinely at bedtime is often helpful. Orally given xanthine preparations have been much less effective in my experience.

When an attack occurs, the patient will prefer to sit upright or lean forward on a support. An injection containing 10 to 20 mg. of morphine sulfate should be given subcutaneously or intramuscularly, or if the patient is in great distress, 5 mg. may be given intravenously. Oxygen should be administered at a rate of 8 liters per minute by mask or nasal catheter. The gas may be bubbled through 50% ethyl alcohol to reduce foaming if expectoration is copious and frothy. Positive-pressure delivery of oxygen has theoretical virtue, but it is often too distressing for the recipient. Rotating tourniquets should be applied to the extremities to effect an acute reduction of the venous return to the heart. The resulting fall in venous pressure is often associated with a reduction of systemic blood pressure, commonly elevated during an attack to levels above those usual for the patient. The same effects (reduction in venous pressures and peripheral resistance) have been reported after the rapid intravenous injection of 2.5 to 5 mg. of hexamethonium (Bistrium; Esomid; Hexameton; Hiohex; Methium) chloride or 100 to 200 mg. of tetraethylammonium (Etamon) chloride. I have had little experience with this procedure. From the reports, it should not be followed if hypotension is present or if a recent infarction or angina is present. Methoxamine (Vasoxyl) hydrochloride or levarterenol (Levophed) bitartrate ought to be at hand for use if necessary. An intravenous injection of aminophylline (0.5 Gm. diluted to 50 cc. in 5% dextrose and injected at a rate of 10 cc. per minute) often gives immediate and impressive, though often very transient, relief. Ouabain given intravenously (a maximum of 0.5 Gm. followed if necessary by 0.1 mg. hourly for three doses) and lanatoside C (a maximum initial dose of 0.8 mg.) are effective therapeutic agents when the heart rate is rapid (over 130) and when the patient has not been digitalized. When the ventricular rate is very rapid, these drugs may be lifesaving; otherwise the state of grave peril can usually be controlled by the other measures described, and digitalization can be carried out with greater safety at a slower rate with orally given digitalis preparations. If a large pleural effusion is present on one or both sides, thoracentesis should be performed unless the other measures are promptly effective. When acute distress of the pulmonary edema has been relieved, recurrences may be averted by the administration of a mercurial diuretic.

During the past several years the management of congestive heart failure has improved. In general, this is attributable to better diagnosis and more skillful application of measures that have long been in use. New surgical techniques and a few new drugs have been dramatically helpful in solving certain specific problems. Certain drugs and procedures have made therapy easier and therefore more effectively administered. Although the experienced physician will find few, if any surprises in this report, perhaps he will be reminded of the opportunity to apply diagnostic and therapeutic tools that have been laid aside.

Am. Med Assoc. 164:659 (June 8) 1957.

Barnstead Briefs

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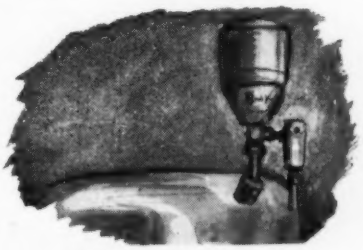

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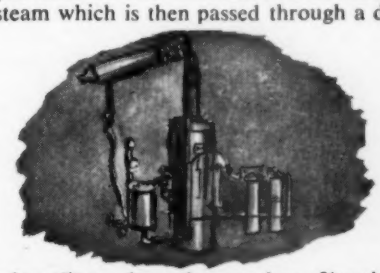

mineralizer, through a carbon filtration unit and then is introduced into the evaporator of the still. Final distillation removes traces of bacteria, organic matter, etc. Write for Bulletin #145 to: Barnstead Still & Sterilizer Co., 31 Lanesville Terrace, Boston 37, Mass.

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LETTERS

Appreciation for Law Issue

DEAR SIRS: I have just received my May-June issue of THE BULLETIN and I must commend Dr. Archambault on his excellent article on "The Law of Hospital Pharmacy." I have accumulated issues of THE BULLETIN since 1945. Many of the articles have been good; more have been excellent, but it is impossible to find words to express my feeling for this past issue. It seems that every issue has so much pertaining to our profession that it is impossible to leave the copy alone until every word has been read and reread.

Is it going to be possible for us to receive reprints of the articles on "The Law of Hospital Pharmacy," and "Suggested Regulations for Handling Narcotics in Hospitals," for distribution to our administrators and for our files?

The organization should extend a vote of thanks to those concerned in making THE BULLETIN one of the best of all pharmaceutical journals.

EDWARD F. CROUMEY, *Chief Pharmacist*
The Mary Fletcher Hospital
Burlington, Vermont

EDITOR'S NOTE: Reprints of the above mentioned articles are available from the Division of Hospital Pharmacy, 2215 Constitution Ave., N.W., Washington 7, D. C. The prices are as follows: "The Law of Hospital Pharmacy"—Single copies 50¢ each; Ten or more copies 35¢ each. "Suggested Regulations for Handling Narcotics in Hospitals"—Single copies 25¢ each; Ten or more copies 15¢ each.

DEAR SIRS: THE BULLETIN is always interesting and worthwhile, but I found the current May-June issue particularly so. I especially would like to have a couple extra copies of George Archambault's article on hand. Would you please send us two additional copies of this issue. Our check for $1.50 is enclosed.

PARKE RICHARDS, JR., *Manager*
Hospital Department
Hoffmann-La Roche Inc.
Nutley, New Jersey

DEAR SIRS: My issue of the May-June number of THE BULLETIN of the ASHP is a beautiful piece of work and most valuable . . . Permit me to take this opportunity to congratulate you and the other members of the staff for getting out so fine a book. Besides being of great worth to us as individual pharmacists, it reflects credit to our profession.

ARTHUR SUMLINER, *Pharmacist*
Camarillo State Hospital
Camarillo, California

DEAR SIRS: In the forthcoming *N.A.B.P. Bulletin,* we are pointing to the attention of Boards of Pharmacy your latest issue of THE BULLETIN OF THE AMERICAN SOCIETY OF HOSPITAL PHARMACISTS which will be of special significance to them in their duties as members of law enforcement agencies.

The article entitled "Legal Requirements for Hospital Pharmacies," contributed by Mr. Grettenberger of the Michigan Board should be especially helpful to members of the Board since this is becoming a problem of increasing importance. The other two articles, "The Law of Hospital Pharmacy," by George F. Archambault and "Suggested Regulations for Handling Narcotics in Hospitals," by Arthur W. Dodds, will also be mentioned as sources of information to Board members. May we congratulate you for this special issue pertaining to the laws of hospital pharmacy.

FRED T. MAHAFFEY, *Editor*
N.A.B.P. Bulletin
National Association of
Boards of Pharmacy
Chicago, Illinois

Appreciates Services

DEAR SIRS: I am assigned to the Madigan Army Hospital as the Chief of Pharmacy Service and am a member of the Therapeutic Agents Board. This is the military version of the Pharmacy and Therapeutics Committee . . . In connection with this, I would like to have a reprint of the article entitled "The Hospital Formulary," which appeared in THE BULLETIN some time ago . . . I would also like to have a copy of the *Minimum Standard for Pharmacies in Hospitals.*

I want to thank you for your service and say that I enjoy reading the *A.Ph.A. Journal* and THE BULLETIN and receive many excellent suggestions from them.

GERARD L. PIERCE, *Captain,* MSC
Chief, Pharmacy Service
Madigan Army Hospital
Tacoma, Washington

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EDITORIAL

Parenteral Solutions Prepared In Hospitals

by DON E. FRANCKE

An article appearing in this issue of THE BULLETIN (page 573) reports the results of a study of parenteral solutions prepared in hospitals. The authors found that 36 percent of the solutions of sodium chloride and 52 percent of the solutions of dextrose did not meet the labeled requirements as to strength. They also found that all solutions, with a single exception in each category, met the requirements as to sterility and absence of pyrogens.

In the same study, the authors observed that one of the five commercial solutions assayed did not meet the official requirements. Applying the same percentage figures, this result indicates that 20 percent of the commercial solutions tested were not within the required range of labeled potency.

As the authors point out, "This is a sad reflection on the care and technics used in compounding and manufacturing the solutions." However, of the solutions made in hospitals, the authors also state "The personnel manufacturing the parenteral solutions consisted not only of pharmacists and pharmacy-supervised operators *but in many instances of laboratory technicians and central supply staff.*"*

It would have been interesting and informative if the authors had included in their questionnaire to the hospitals, a question relative to who is responsible for the preparation of the intravenous solutions. Were the solutions which did not meet labeled requirements made by pharmacists or by other personnel in Central Supply, or both? What percentage of the solutions in question were prepared by pharmacists and what percentage were made by others?

However, these questions are not raised to evade the implications of the study. The authors have done a service to hospitals by performing this study and making its results known. On the other hand, it should not be inferred from the study that the results apply to solutions made by pharmacists. In fact, the authors did not ask this question and thus this conclusion cannot be drawn from the results reported. It would be safe to assume that a far higher percentage of solutions made by pharmacists met the requirements for labeled strength than those prepared by non-pharmaceutically trained personnel in other departments. If the percentage of inaccurate solutions prepared in hospitals seems high (36 and 52%), so does the percentage of inaccurate solutions (20%) prepared by commercial sources.

This study emphasizes two important points. Hospital administrators should make a critical evaluation of the hospital's sterile solution program. If the solutions are prepared in a department other than the Pharmacy, their preparation should be placed under the supervision of a pharmacist in accordance with the Minimum Standard for Pharmacies in Hospitals. In addition, hospital pharmacists should make a critical evaluation of their technics and procedures used in the preparation of parenteral solutions. Proper control procedures should be instituted (see Controls in a Sterile Solutions Program page 578). Since most of the errors reported in the study of parenteral solutions made in hospitals were of a quantitative nature, reference should be made to the valuable articles by Goldstein and Mattocks (*J. Am. Pharm. Assoc. Pract. Pharm. Ed. 12*: Apr. 214; May 293; June 362; 1951) which gives detailed procedures for testing the accuracy of prescription and laboratory balances.

Accuracy has always been one of the most important characteristics of a pharmacist. Proper technics of weighing and measuring are among the first fundamentals taught the beginning student in pharmacy. There is no excuse for the poor quantitative results reported in this study. They can be readily eliminated by the use of proper technics and control procedures.

*Editor's italics

THE AMERICAN HOSPITAL ASSOCIATION was established in 1898. Its purpose is "to promote the public welfare through the development of better hospital care for all people." The Association is unique in the fields of national organizations in that its membership consists primarily of institutions rather than individuals.

Historical

This uniqueness was a development in the growth of the Association through the years and a reflection of the increasing importance of its role as the national representative body of hospitals. When the organization that was to become the American Hospital Association was founded in 1898, it was called the Association of Hospital Superintendents of the United States and Canada and consisted of 11 personal members. In 1906, when the name was changed to the American Hospital Association, the membership was still entirely on a personal basis. It was not until 1918, when the membership consisted of 1,250 personal members, that it was voted to accept institutional members. During this first year of institutional membership, 98 hospitals joined the Association. From this modest beginning, the Association continued to grow rapidly, to the present total of 6,975 institutional members, of which 5,420 are hospitals in the United States and Canada. In addition, more than 60 foreign hospitals belong to the Association. Member hospitals include short-term general and special institutions, long-term hospitals, clinics and dispensaries, and hospitals in the planning or construction stage. Other institutional members are Blue Cross Plans, allied organizations in the health field, and hospital auxiliaries. Personal members of the Association, including hospital administrators, hospital personnel and others engaged in or interested in hospital and health work, now number 4,500. (A number of hospital pharmacists are personal members of the Association.)

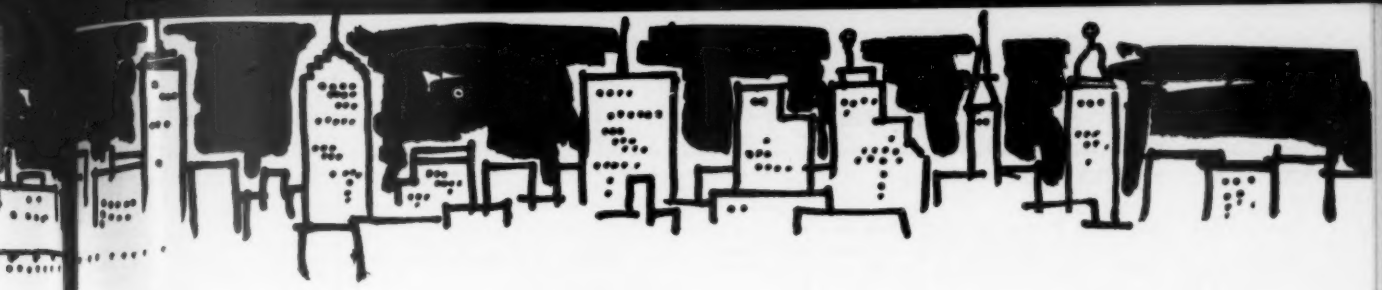
The Association's program is aimed at meeting the needs of all hospitals regardless of their size, type of clinical service offered, or ownership. As every hospital administrator knows, Association membership provides services that cannot be carried out economically by any one hospital acting alone. The goals of the Association are to help hospitals extend their services to the public and to increase their efficiency and quality of service. The Association accomplishes this in many ways.

Organizational Structure

The organizational structure of the Association is designed to provide for the most complete representation of members and the most extensive

Presented at the Annual Meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, House of Delegates Section, on April 28, 1957.

JOSEPH A. ODDIS is Staff Representative in Pharmacy, Council on Professional Practice, American Hospital Association, Chicago, Illinois.



THE AMERICAN HOSPITAL ASSOCIATION AND HOSPITAL PHARMACY

by JOSEPH A. ODDIS

study and activity in all phases of hospital work. The final policy-making body of the Association is its House of Delegates, composed of representatives selected by members of the Association in each state, territory, and Canadian province. The House of Delegates elects the officers, Board of Trustees, and delegates-at-large of the Association. The seven councils of the Association: Administrative Practice, Association Services, Government Relations, Hospital Auxiliaries, Hospital Planning and Plant Operation, Prepayment Plans and Hospital Reimbursement, and Professional Practice—and the Blue Cross Commission carry on a wide variety of activities, programs and studies in their particular areas. The chairmen of these groups comprise the Coordinating Committee of the Association, which meets four times a year with the Board of Trustees. The chairmen and members of these councils are appointed by the President of the Association with the approval of the Board of Trustees.

In addition to the councils, there are 48 committees which are concerned with specific details ranging from disaster planning to laundry management. The councils and committees of the Association are composed of hospital administrators, hospital department heads and experts from allied fields. Close to 300 individuals are active in these councils and committees each year. In the course of a year, more than 1,000 hospital career workers serve on the deliberative bodies of the Association, assist in planning and presenting educational institutes, and participate in other Association activities. This breath of representation helps to keep the Association in close touch with the operating problems of hospitals.

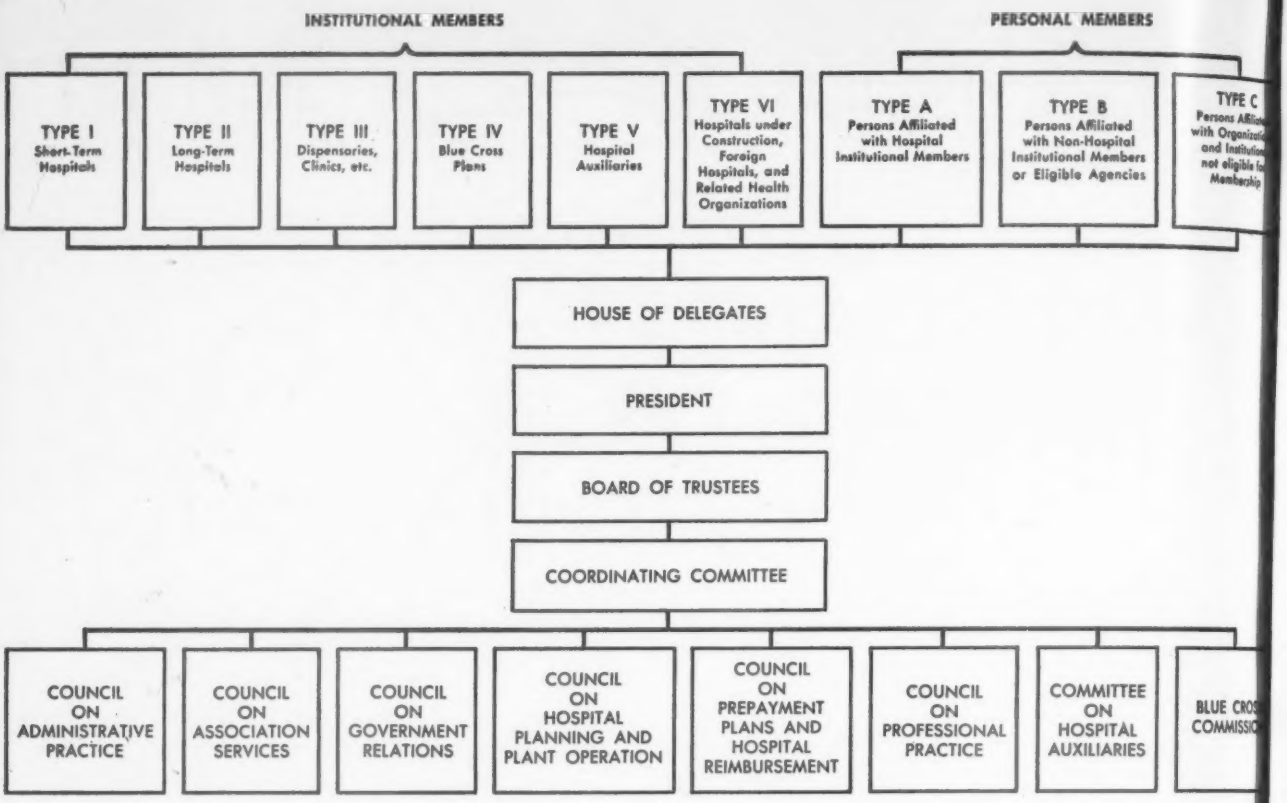
Publications

Among the media and methods ordinarily used to bring the services and programs of the Association to the membership, are the official publications:

Hospitals, Journal of the American Hospital Association, is published semi-monthly and is written for administrators, department heads, and others concerned with the administration of hospitals, the techniques of hospital operation, and the planning and construction of hospitals. The August 1st issue of *Hospitals* appears in two parts —the second part is the annual *Guide Issue* which contains the latest statistics in the hospital field and lists of hospitals and related organizations in the health fields. Pharmacy articles which are published appear under the section on Professional Practice. A recent article on hospital pharmacy which appeared in this journal was prepared by Dr. George F. Archambault and described pharmacy accidents and their prevention.

Trustee is the Association's pocket-sized journal for members of hospital governing boards.

This Month at the American Hospital Association is an informal newsletter sent each month



without charge to all institutional and personal members. It informs the members of current activities within the Association's councils and committees and contains a message from the director.

The Auxiliary Newsletter is published for hospital auxiliaries holding institutional membership in the Association. Serving as a means of communication between the members, it helps them plan projects and services that will best meet the needs of their hospitals. Featured in a future issue of the newsletter will be an article by Paul Parker on hospital pharmacy.

Library Service

The Association's library, the Asa S. Bacon Memorial, houses the most comprehensive collection of hospital literature in the world. It contains 12,500 books, complete sets of bound hospital and nursing periodicals, and more than 100 file drawers of magazine articles, classified by subject. The library also maintains collections of such materials as annual reports, booklets for patients, hospital bulletins, etc. Requests for assistance are answered by informational letters, bibliographies, or the loan of "package libraries." The individual package—consisting of the most pertinent books, magazine articles, and pamphlets —is loaned for one month. Association members need only state the question on which they need information, and the A.H.A.'s library staff selects appropriate references and sends them on loan. Generally, this material is supplemented with a personal letter from a member of the headquarters staff. Hospital pharmacists may partake of this library service even though they may not be personal members of the Association, provided the hospitals in which they are employed are institutional members of the American Hospital Association.

Annual Convention

The annual convention of the Association, the biggest hospital meeting in the world, is attended by some 12,600 representatives of the hospital and health fields. Here administrators, department heads, trustees, auxiliaries, and other representatives of hospitals are brought up-to-date on trends in hospital operations. Talks and panel discussions constitute the program, supplemented by the Hospital Merchandise Mart of more than 500 commercial and technical exhibits which bring together in one place all the latest developments in hospital equipment and supplies. Tentative plans for this year's convention in Atlantic City call for three roundtable discussions on mat-

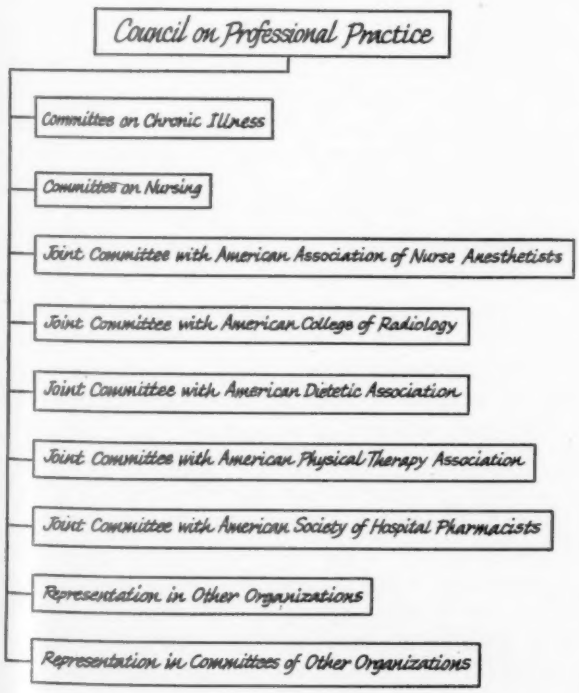
ters pertaining to hospital pharmacy. Such subjects as "Formulary Systems in Hospitals," "Pharmacy Service in the Smaller Hospital," and "Providing Pharmaceutical Services after Normal Pharmacy Hours" are currently being considered.

Research

Research by the Association has become an activity of increasing size and importance in recent years. During 1956 and the early part of 1957, grants of more than $3,500,000 were made to the Association for various research projects. Projects undertaken using these grants include studies of hospital licensing laws, hospital planning and design, and the future need for hospital facilities. Of interest is the most recent grant for the purposes of studying cardiovascular drugs.

Council Activities

Each council in the Association is concerned with specific areas of hospital activity and carries on programs covering these areas. The Council on Administrative Practice, for example, is concerned with such activities as bookkeeping procedures in hospitals, cost finding, insurance, laundry management, etc. The Council on Government Relations, as the name implies, keeps in close touch with legislation and proposed legislation affecting hospitals and the health field. Headquarters for this Council is the Association's Washington Service Bureau in Washington, D. C.


Council on Professional Practice
Committee on Chronic Illness
Committee on Nursing
Joint Committee with American Association of Nurse Anesthetists
Joint Committee with American College of Radiology
Joint Committee with American Dietetic Association
Joint Committee with American Physical Therapy Association
Joint Committee with American Society of Hospital Pharmacists
Representation in Other Organizations
Representation in Committees of Other Organizations

Council on Professional Practice

The Council on Professional Practice is of particular importance to hospital pharmacists, since this is the Council which is concerned with all professional endeavors of hospital operations. Dr. Sarah H. Hardwicke, Secretary of this Council, is familiar to many of you, having appeared before this body in recent years and having participated in various pharmacy meetings and educational programs. Sharing responsibility for the Council's activities is Dr. LeRoy E. Bates, who is Associate Secretary of the Council and also well-known to many of you. Other members of this Council, include representatives in the areas of nursing, dietetics, medical records and pharmacy.

The areas of interest to this Council are many and certainly too numerous to name in entirety. This Council presently is carrying on active programs in four committees dealing with nursing, chronic illness, etc.

In addition, the Council enjoys friendly and cooperative relations in its dealings with some 12 national organizations through the medium of Joint Committee meetings. Such joint committees presently exist with the Association of Nurse Anesthetists, American College of Radiology, American Dietetic Association, American Physical Therapy Association, AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, and others. Liaison is also maintained by representation of the Council in other organizations and in committees of other organizations. Such representation exists in fields of Mental Illness, Intern Matching Programs, Post-graduate Medical Education, and some 21 other areas.

One of the prerequisites for accreditation by the Joint Commission on Accreditation of Hospitals is that hospitals be listed in the Guide Issue of *Hospitals*, J.A.H.A. Since 1955 when the Association commenced the listing program, this activity has been coordinated by the Council on Professional Practice and the Association's officers and staff are all requested to visit 20 hospitals each year for listing purposes. These visits are coordinated with other work during the course of travel. The council employs 5 (1 Canadian) physicians, however, whose sole responsibility is the surveying of hospitals for accreditation. These field representatives have been responsible for 41 percent of all surveys by the Joint Commission on Accreditation of Hospitals since its establishment in early 1953.

Hospital Pharmacy

In 1935, the Council on Professional Practice of the A.H.A. gave serious thought to the practice of hospital pharmacy in the nation's hospitals. A

resolution presented and adopted at the annual meeting proposed that a "committee on pharmacy be formed to study the operation of hospital pharmacies and to develop the minimum standards for such department for the guidance of the hospital field." This was the first significant recognition by the A.H.A. of hospital pharmacy as "one of the more important professional departments."

It must be pointed out, however, that as early as 1925, a group of hospital pharmacists approached the A.H.A. with a desire to affiliate with this organization and have a section on pharmacy at the annual meeting. This request was refused and it was suggested they have their section in the A.Ph.A. convention.

In 1936 the Committee on Pharmacy announced that it planned to send out a number of questionnaires during the year and to submit a tentative draft of standards for pharmaceutical service in the hospital.

It was in this year also that the first sub-section on hospital pharmacy was established in the A.Ph.A. which resulted in a sub-section meeting the following year at the New York City Convention. It is interesting to note that the rising importance of hospital pharmacy and the increasing recognition which was being accorded this specialty coincided with the approaching age of chemotherapy.

In 1937, a memorable report was submitted by the Committee on Pharmacy of the A.H.A. at the annual meeting. The report was rather lengthy, 32 pages in all, but very thorough, dealing with such important matters as policy, standards for operation, the pharmacy committee, the hospital formulary, physical aspects of the pharmacy, equipment, economics, legal matters, the special hospitals of the time, and many others. This Committee was composed of seven members, five from the medical profession and two from other areas of hospital work. It was unfortunate that so little emphasis was attached to this outstanding and far-reaching report. It has taken almost two decades to realize the full significance of the report, many aspects of which are just beginning to come to focus.

During this time, the American College of Surgeons formally approved the Minimum Standards For Hospital Pharmacies, as proposed, and used this as a guide in their program of inspecting hospitals.

The following year, R. H. Stimson, a pharmacist-speaker at the annual meeting of the A.H.A., stated: "I feel that we should have a national association of hospital pharmacists and, in my opinion, this association should be affiliated with the A.H.A. or A.M.A."

During the ensuing years, between 1938 until 1943, the Committee on Pharmacy of the A.H.A. continued to present programs of a high caliber at the annual meetings. Although the 1937 report of the Committee had been relatively ignored, some consideration was still being given to the possibility of developing a workable hospital pharmacopeia. It was in 1942, however, that the idea of such a pharmacopeia was abandoned and emphasis was focused on the preparation of a manual outlining the basic principles and procedures of good pharmacy practice.

Unfortunately, in 1943, world conditions were such that the Committee on Pharmacy Practice and Formulary, as it was then known, was suspended for the duration, and preparation of all manuals was discontinued. Even world conditions, however, could not impede the progress of hospital pharmacy, and about this time a small group of hospital pharmacists had firmly established the foundation for the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, the story of which you all know so well.

The year 1946 marked the renaissance of the Committee on Pharmacy of the A.H.A. Dr. Don Francke was a member of the Committee. The first institute on hospital pharmacy, conducted by the A.H.A. in cooperation with the A.Ph.A. and ASHP, was held during this year at Ann Arbor. One hundred and forty-five pharmacists participated to make this a highly successful venture.

Later Developments

Things began to happen now. In 1947, the A.H.A. was invited to appoint a representative to the Committee on Minimum Standards of the ASHP. In 1948, the A.H.A. was invited to send a representative to the Policy Committee of the Division of Hospital Pharmacy of the A.Ph.A. In 1950, the A.H.A. adopted the Minimum Standard for Pharmacies in Hospitals as proposed by the Division of Hospital Pharmacy of the A.Ph.A. and ASHP. In 1953, three recommendations were submitted by The Committee on Pharmacy of the A.H.A. for consideration. It was recommended that:

1. A hospital pharmacist be appointed to the staff of the A.H.A.
2. A joint committee be established with the ASHP to promote closer liaison and provide a means of studying matters of mutual interest.
3. A manual of practice in hospital pharmacy be developed.

All three recommendations were accepted. The Joint Committee held its first meeting on November 23, 1953, in Chicago. The SOCIETY'S rep-

resentatives to this Joint Committee were Allen Beck, Grover Bowles, Don Francke, and Gloria Francke. In 1955, approval was granted for the writing of a manual, and a hospital pharmacist was appointed to the A.H.A. staff in 1956.

Joint Committee A.H.A.—ASHP

As you can see from the chart, the Joint Committee is composed of leading hospital pharmacists and administrators. The Joint Committee is composed of eight voting members—four from each organization. Ex officio membership consists of the president of the A.H.A., the president of the ASHP, and representatives of the staff of each organization. The purpose of the Joint Committee is to serve as an agency to the parent organizations and to discuss and resolve problems of mutual interest.

Recommendations of the Joint Committee are advisory to, and not mandatory upon, the parent organizations. The Joint Committee not only originates actions; but may, at times, receive actions for consideration from the parent organizations.

The problems and subjects which are discussed at these meetings are varied and deal with all areas of hospital pharmacy operations. Some of these areas are perennial, while others are matters of current interest.

A few of the subjects under current consideration are:

1. Use of tax-free alcohol and spirituous liquors in hospitals.
2. Safety practices and common accidents in pharmacy.
3. Pharmacy service in smaller hospitals.
4. Manual on Hospital Pharmacy.

Recently, the Joint Committee prepared a "Guide for Inspection of Pharmaceutical Service" which was approved and forwarded to the Joint Commission on Accreditation of Hospitals for their consideration. An item receiving considerable attention by the Joint Committee at present, deals with the use and proper handling of investigational drugs in hospitals.

It is reasonable to say that the accomplishments which can be achieved by this joint effort far exceed the singular gains that might be attained by each organization on an individual basis. The fine relations which have existed in the past in all endeavors, I am certain, will continue to flourish as time goes on.

The establishment of a position for a hospital pharmacist on the staff of the A.H.A. is significant in that recognition has been given to the importance of the hospital pharmacist in the modern concept of the hospital health team. The immediate primary concern of the A.H.A. staff representative in pharmacy is the writing of a Manual on Hospital Pharmacy. Broad headings which will be treated in this Manual are:

1. Objectives of the Hospital Pharmacy
2. Organization
3. Administrative Policies
4. Departmental Policies
5. Physical Planning
6. Functions
7. Legal Reqirements
8. Special Problems in Smaller Hospitals
9. Special Projects

Other responsibilities of this position are:

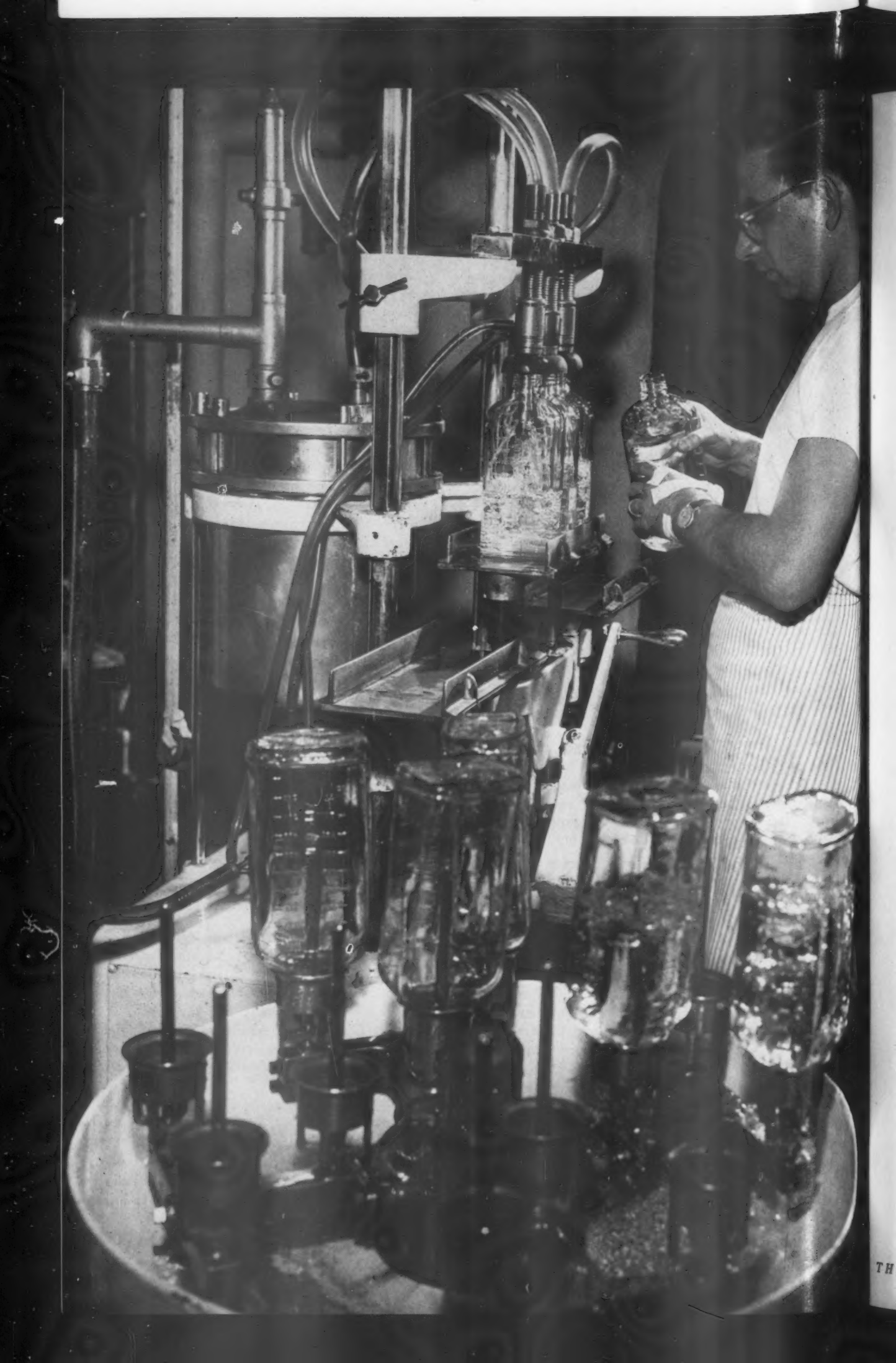
1. Acting in the capacity of coordinator for the two annual institutes on hospital pharmacy.
2. Review of articles for publication in *Hospitals*.
3. Answering of correspondence pertaining to pharmacy matters.
4. Carrying out the duties of Secretary of the Joint Committee.

Hospital pharmacists are encouraged to use the facilities of the A.H.A. when necessary, particularly the services of the library in matters dealing with hospital pharmacy and hospital administration in general.

Personal membership for hospital pharmacists in the American Hospital Association is available, if desired. President Parker has already brought this to the attention of hospital pharmacists in a recent issue of THE BULLETIN. Personal membership brings publications previously mentioned, various publications which appear from time to time, and all routine general mailings designed to keep the membership informed of current happenings in the hospital field.

Conclusion

I have attempted to outline the function and scope of activity within the American Hospital Association and to bring to your attention the role which hospital pharmacy has played in its framework. The progress which has been made is evident. The establishment of the Joint Committee for liaison between the two organizations has proved to be successful. Had the request of the hospital pharmacy group of 1925 for affiliation with the American Hospital Association been granted, the course of events would possibly have been entirely different. Just what course would have been followed, had this occurred, is now a matter for speculation only.



A STUDY OF *parenteral solutions* MADE IN HOSPITALS

by Irene Olynyk, P. Belcastro, and G. J. Sperandio

The preparation of large volume parenteral solutions in hospitals has become a controversial subject. The hospital pharmacist is confronted with the decision of preparing intravenous solutions or purchasing them from a commercial producer. If he manufactures the solutions himself, not only should he be prepared to supply special formulations when necessary but he should also effect a substantial saving to his institution.[1] The commercial firms subject their preparations to stringent tests for pyrogens, sterility, and potency as it is mandatory that the solutions conform to official standards. In initiating the manufacture of parenteral fluids in the hospital the pharmacist must take this into consideration and when he replaces commercial solutions with his own, his solutions must be of equal or superior quality. The development of small scale parenteral solution equipment has encouraged more hospitals to undertake a solution manufacturing program. Claims have been made that with the proper use of this equipment pyrogen-free solutions are assured.[2]

The threat of thermogenic substances in infusion fluids has been the greatest deterrent to those who have contemplated manufacturing intravenous solutions. The study of pyrogens has paralleled the increasing use of large volume injections. The term *pyrogen* is now limited to substances which elevate the temperature and are obtained from living bacteria.[3] Seibert[4, 5] in 1923 conclusively proved that the pyrogenicity of distilled water was due to a filterable, heat-stable, bacterial by-product. Pyrogens have been found to be associated more often with gram negative than with gram positive organisms.[6] Ginger and co-workers[7] have shown the composition of pyrogenic polysaccharides to consist of hexosamine, an unclassified reducing sugar and a non-reducing carbohydrate fraction but they were unable to correlate pyrogenicity with the existing composition data. Similarly there appears to be no relationship between the pathogenicity of an organism and its thermogenic power.[8] The many salient points of pyrogen testing will not be discussed here as Tennent and Ott[9] and other workers[10, 11] have treated the various aspects of the test in great detail.

Irene Olynyk and P. Belcastro were Graduate Students and G. J. Sperandio is Associate Professor of Pharmacy, School of Pharmacy, Purdue University, Lafayette, Ind.

Presented at the Annual Meeting of the American Society of Hospital Pharmacists held April 24, 1956 at Detroit, Mich.

Received from the research laboratories of Purdue University School of Pharmacy, Lafayette, Ind.

Purpose of Study

This study was undertaken among the hospitals in the United States and Canada for the purpose of evaluating some solutions now being prepared in hospitals and to gain knowledge of the techniques employed. It was felt that the information obtained would be useful to the pharmacists who might be considering the manufacture of intravenous solutions. In addition it was hoped that the results could be further interpreted to permit a prediction as to whether the hospital pharmacist can safely prepare his own parenteral solutions.

Experimental

Letters requesting one liter of isotonic sodium chloride solution and one liter of 5 percent dextrose solution in distilled water were sent to 110

FIGURE 1. SURVEY QUESTIONNAIRE

PLEASE COMPLETE THE FOLLOWING QUESTIONNAIRE AND RETURN WITH SOLUTIONS

1. What is the size of your hospital_____beds?
2. Which of the following methods of preparation do you use?
   Fenwal_____American Sterilizer_____Which other type _____
3. Is the distilled water that is used for the parenteral solutions, single_____double_____triple_____distilled?
4. What length of time is allowed to elapse between the distillation of the water and the actual autoclaving_____hours?
5. Which of the following makes of stills are used?
   Barnstead_____ Wilmot-Castle_____ Precision_____ Which other type_____?
6. What is the capacity of the still_____gallons per hour?
7. What type of balance is used for weighing the ingredients?
   Analytical_____Torsion_____Which other type_____?
8. Is the same operator employed for preparing the solutions_____?
   Is the job rotated between two people_____more_____?
9. In autoclaving, how much time_____minutes, what temperature_____°C. or F. and lbs._____pressure is used?
10. What type of room is used for this purpose and are any special conditions maintained?_____
11. What procedure is used for cleaning glassware and other equipment?_____
12. Which of the following controls are used:
    Sterility—every batch_____never_____periodically_____
    Pyrogen—every batch_____never_____periodically_____
    Potency—every batch_____never_____periodically_____
13. Remarks _____
14. Do you wish to have a report on your solutions?_____ yes_____no?

Control number_____ (do not use this space, please).

hospitals known to prepare solutions and to 5 commercial firms. In obtaining the two different solutions from each source, it was felt that a check could thus be made on two different lots of distilled water as well as on the two different ingredients. A questionnaire was included with the letter to obtain some pertinent facts as to the size of the hospital and certain details of the procedures employed. Questions were asked concerning the type and size of still, autoclave, balance, etc. as well as the cleaning, manufacturing, sterilizing and control techniques. Code numbers were assigned to each bottle of solution received, for use in the publication of the results. The questionnaire is shown in Figure 1.

Of the 110 hospitals contacted 41 percent replied, but not all the hospitals replying to the questionnaire sent solutions for testing. Solutions were received from 26 hospitals which is equivalent to a 23.6 percent response. The 14.7 percent of the hospitals who replied but did not participate stated that they did not prepare their own solutions at the time.

These 26 hospitals participating in the project may be divided into four groups according to their bed capacity:

1,000 beds or more	4
501 - 900 beds	6
300 - 500 beds	13
150 - 250 beds	3

An attempt was made to correlate the questionnaire data with the test results obtained and to note if any valid relationships could be established between the two but this was unsuccessful. The replies revealed many variations in the manufacturing procedures employed. The equipment such as stills, balances, autoclaves, etc., as well as conditions for distilling water, weighing, sterilizing, etc. demonstrated a wide range of variables.

Each solution was subjected to three tests: a sterility test, a check for pyrogens, and a quantitative assay for chemical strength.

During the study all the glassware which required sterility was subjected to a cleaning procedure to render it sterile and pyrogen-free. After soaking in a 1 percent acid solution for one-half hour, it was washed in detergent solution, rinsed three times in tap water, then rinsed in distilled water and sterilized by dry heat at 250°C. for one-half hour.

The sterility inoculations[12] were made in a CBR unit* immediately before the pyrogen testing. The unit consists of a closed-in cabinet with an ultraviolet light to sterilize the enclosed working areas. The solution containers were wiped with benzalkonium chloride solution (1:1,000) before placing them into the unit. A sterile syringe with a 3 inch hypodermic needle was used to transfer 10 ml. of the solution into each of three tubes containing 40 ml. of Fluid Thioglycollate Medium and each of three tubes of Sabouraud Liquid Medium.** The inoculated media were incubated for seven and ten days respectively. If at the end of the stipulated periods no growth had appeared, the solutions were considered to have met the requirements for sterility. The *United States Pharmacopeia* designates the use of thioglycollate medium because it supports the growth of aerobic and anaerobic organisms while the Sabouraud medium is favorable for the growth of yeasts and molds.

The U. S. P. pyrogen test[12] was used for the detection of thermogenic substances. Albino rabbits of both sexes were used, weights ranging from 1,700 to 4,299 grams. The animals were

injected with 2 to 5 ml. of pyrogen-free normal saline solution in order to accustom them to the injections. They were then subjected to a "sham test"[13] wherein four temperature recordings were obtained but the injection was omitted. A two-minute period was used to obtain the rectal temperature, the rabbit being held on the operator's lap.[14, 15, 11] This time had been previously determined as ample to obtain the maximum temperature response. The thermometers were stored in benzalkonium chloride solution (1:1,000) to prevent the spread of any possible infection. After the normal or initial temperature was recorded, the animal was immobilized in a towel and placed in an open rabbit box. The solution, warmed to 37°C., was injected into the marginal ear vein. A dose of 10 ml. of solution per Kg. of body weight was administered by means of a sterile 50 ml. syringe and a 22 gauge hypodermic needle within a period of 1 to 2 minutes. Seibert[4] reported that there is no relationship between the speed of injection and the degree of febrile response. Temperature readings were made at hourly intervals for three hours after the injection. The animals were never used oftener than once every forty-eight hours, and after a pyrogenic response a two-week recovery period was allowed before the rabbit was again used.[13]

After all the solutions had been tested, a typical pyrogen test was carried out on every animal, replacing the intravenous infusion with an injection containing known pyrogens.* This step demonstrated the sensitivity of each rabbit to pyrogens.

The sodium chloride assays were made by titrating the solutions against 0.1N silver nitrate solution using dichlorofluorescein as the indicator.[16] This method gave a readily observed endpoint.

The official polarimetric method was used for the dextrose assay.[12] The mean of ten vernier readings was observed for each solution. The values of the samples in grams were determined by multiplying the angular rotation observed in degrees by 1.0425.

RESULTS

Sterility Tests

Only one solution (number 104B) exhibited growth after incubation, and this solution had contained a mold when it was received. All of the

*Kewaunee Mfg. Co., Adrian, Mich.
**Difco Laboratories, Detroit, Mich.

*Positive pyrogen solution obtained from Mr. H. C. Sp:uth, Manager, Bioassay Laboratories of Abbott Laboratories.

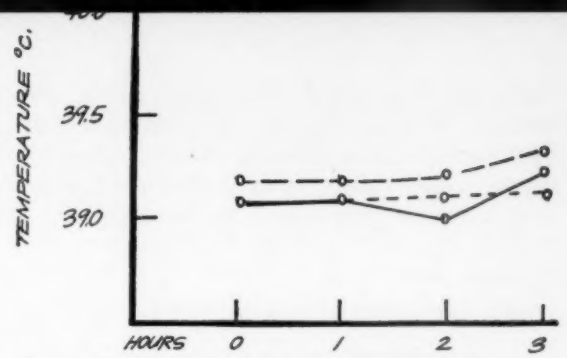


FIG. 2. Rectal temperature response of rabbits injected with a non-pyrogenic solution.

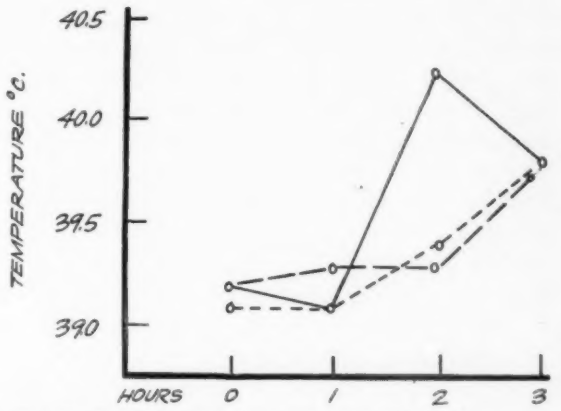


FIG. 3. Rectal temperature response of rabbits injected with the pyrogenic solution.

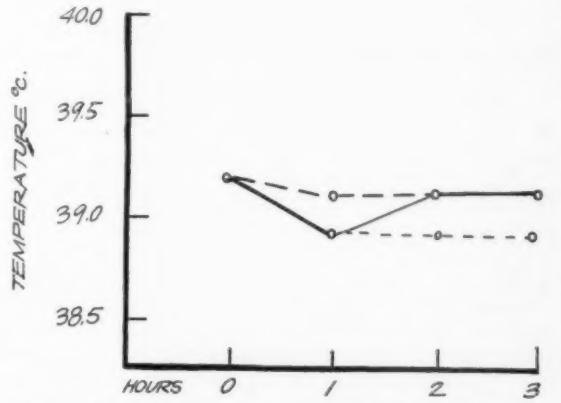


FIG. 4. Rectal temperature response of rabbits injected with a non-pyrogenic solution.

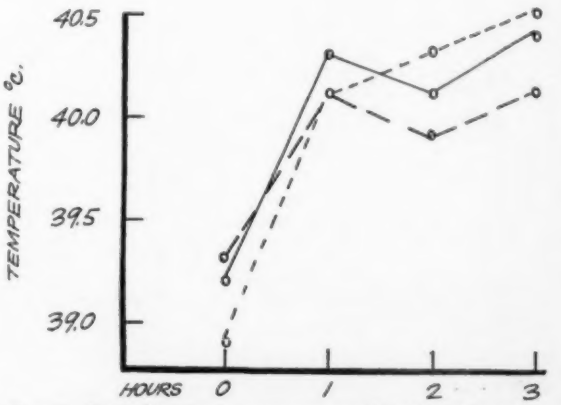


FIG. 5. Rectal temperature response of rabbits injected with a positive pyrogenic solution (control).

other solutions tested were sterile. The sterility tests proved that adequate care had been used by the hospitals in autoclaving their solutions. This would indicate that when proper conditions are maintained sterile solutions can be expected.

Pyrogen Test

The *United States Pharmacopeia XIV* states "the test shall be considered positive if 2 or 3 animals show an individual rise in temperature of 0.6°C. or more above the normal established for each of these animals." Only one solution (number 124A) was found to be pyrogenic and Table 1 shows that two animals exhibited a temperature rise of over 0.6°C. when injected with this solution. Figures 2 and 4 demonstrate the temperature curves obtained with non-pyrogenic solutions. The pyrogenic solution response is seen in Figure 3 while the positive pyrogen solution (control) is shown in Figure 5. The same three rabbits were used in each case.

TABLE 1. THE THERMOGENIC RESPONSE OF RABBITS INJECTED WITH NON-PYROGENIC AND PYROGENIC SOLUTIONS.

		Rise in Temperature	
		Non-pyrogenic solution	Pyrogenic solution
Rabbit number	1	0.1° C.	0.7° C.
	5	0.2°	1.0°
	7	0.1°	0.4°

Sodium Chloride Assay

The solutions assayed for sodium chloride showed a great variation in strength as can be seen in Table 2.

TABLE 2. SODIUM CHLORIDE ASSAY OF HOSPITAL AND COMMERCIALLY PREPARED SODIUM CHLORIDE SOLUTIONS.

Group I (0.85 percent)*		Group II (0.9 percent)	
Code number	mg./100 ml.	Code number	mg./100 ml.
103A	928.6	201A	943.4
122A	792.6	123A	922.7
107A	851.8	125A	922.7
116A	939.9	101A	940.4
108A	928.7	124A	1005.5
109A	936.4	118A	1135.7
121A	819.2	204A	910.9
112A	928.7	117A	976.0
111A	903.4	202A	916.8
102A	863.6	115A	916.8
120A	808.4	119A	934.6
		110A	908.0
		113A	899.0
		105A	857.7
		104A	905.0
		106A	981.9
		114A	905.0

* 11 hospitals sent 0.85 percent sodium chloride solutions.

Of the 25 hospital-prepared solutions 9 were outside the range of their labeled strength, while all of the commercial solutions were within the official limits. This is a sad reflection on the care and techniques used in compounding and manufacturing the solutions.

Dextrose Assay

The results obtained from these assays were similar to those of the sodium chloride assay and are shown in Table 3.

TABLE 3. THE CONCENTRATION OF DEXTROSE IN HOSPITAL AND COMMERCIALLY PREPARED DEXTROSE SOLUTIONS.

Code no.	Gm./100 ml.	Code no.	Gm. /100 ml.
118B	3.79	109B	5.60
107B	5.66	126B	5.67
112B	6.25	124B	5.52
103B	5.83	105B	5.12
102B	5.21	119B	4.85
204B	5.12	117B	5.35
111B	5.08	116B	5.12
110B	4.92	115B	5.52
123B	5.12	113B	5.04
202B	5.17	203B	4.66
120B	5.21	108B	4.87
122B	4.14	101B	5.62
106B	5.62[a]	114B	5.02
104B	10.86[b]	125B	4.48
121B	5.73[c]		

a. Volume loss—evaporation (?)
b. Ten percent—mold present when received.
c. Probable leak—packing adhering to closure when received.

If the three solutions 106B, 104B and 121B are excluded because of the above noted defects, twenty-three remain, with thirteen of these not meeting the official requirements. One commercial solution did not comply with the United States Pharmacopeia specifications.

Discussion

Seibert[4] stated that the presence of pyrogens is recognized by the character of the curve and the average temperature variation of the test animal. This variation in the pyrogen response is much greater than found in normal variation or in the negative reaction of the same rabbit. With one exception, the results of the pyrogen tests showed that the necessary precautions had been observed by the hospitals concerned to obtain pyrogen-free solutions. In the single solution exhibiting thermogenic activity it would seem that contamination with pyrogens had been introduced at some stage of the preparation of the solution. It should be clarified here that there is no reason to believe that the type of parenteral equipment used had any bearing on producing the pyrogenic solution code number 124A as the other solution sent in by

the same hospital was non-pyrogenic. Three other hospitals using similar equipment prepared non-pyrogenic solutions. It can only be surmised that there had been a break in the meticulous technique required that produced the unsatisfactory solution.

Since 11 of the hospitals sent in 0.85 percent sodium chloride solutions their conformance to the labeled strength rather than the United States pharmacopeial requirements was considered in evaluating the accuracy of the preparation. The official range for the sodium chloride injection is 850-950 mg. percent sodium chloride and if the same percentage allowance were made for the 0.85 percent solutions, their limits would be 803-897 mg. percent sodium chloride. Thus it was found that 36 percent of the solutions were outside their labeled strength. In the case of the dextrose solutions, the percentage outside the official requirements rose to 52 percent. With so much deviation from the required potency one can only assume that adequate precautions for calculations, weighing and other steps during the manufacture of the solutions had not been taken. It is also possible that sufficient allowance had not been made for moisture loss during sterilization since 71 percent of the unsatisfactory fluids were over the maximum strength allowed by the *United States Pharmacopeia.*

The personnel manufacturing the parenteral fluids consisted not only of pharmacists and pharmacist-supervised operators but in many instances of laboratory technicians and central supply staff.

Summary and Conclusions

1. Sodium chloride solutions and 5 percent dextrose solutions were obtained from 26 hospitals and 5 commercial firms in the United States and Canada. They were subjected to tests to determine whether they would conform to the United States Pharmacopeia requirements with respect to pyrogens, sterility, and potency.

2. All but one of the solutions were found to be sterile indicating adequate autoclaving conditions. Only a single solution gave pyrogenic response. This means that the hospitals in this study except for one instance were able to comply with conditions to produce pyrogen-free solutions.

3. The quantitative assay for the sodium chloride and dextrose revealed that the greatest errors occurred in the actual preparation of the solutions. If control assays were conducted routinely any deviation from the desired potency would immediately show the lack of precision or error in the procedure or equipment.

4. A statistically reliable number of samples was not available to predict from this study with any degree of confidence if the hospital pharmacists could prepare satisfactory large volume parenteral fluids. Similarly, due to the variation in the equipment and the techniques used the number of solutions received did not provide sufficient significant information to denote endorsement of any particular method.

5. It is apparent, however, even from this limited study, that certain facts must be recognized if the hospital pharmacist is to manufacture parenteral fluids:

a. Continuous and meticulous attention must be paid to sterility, and if all precautions are met, the hospital pharmacist can prepare sterile solutions.

b. The danger of pyrogens must ever be recognized and some arrangement should be made for pyrogen testing of solutions by qualified personnel.

c. Of equal importance are the basic techniques of weighing and measuring. If these are not actually performed by the pharmacist they should be supervised by him.

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CONTROLS
in a sterile solutions program

by Irene O. Olynyk

The hospital pharmacist has recognized the increasingly important role of parenteral solutions in present day therapy and is endeavoring to provide the desired fluids at minimal cost to the patient and the hospital. Medication administered to the surgical patient typifies this trend—pre-anesthetic sedatives, induction or often total anesthetics, post-operative analgesics and the intravenous feeding of dextrose, electrolytes, protein hydrolysates, vitamins and antibiotics—all administered parenterally as standard procedure to promote a speedy return to better health.

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The increasingly large number of injections used in hospitals represents a substantial expenditure to the institution. The present status of the pharmacist as a member of the health team places greater emphasis on his potentialities. Periodically the Pharmacy Department has requests for solutions which are not available commercially and unless the department is geared to the preparation of sterile solutions, it is generally difficult to supply these requests. Mindful of the savings[1] and preparedness for unusual requests, many more hospitals are undertaking such a manufacturing program.

In replacing commercial preparations which undergo strict controls with respect to sterility, pyrogens, potency and freedom from foreign materials, they must provide medicaments of equal or superior quality. Not only is it important that the injection does not produce any untoward reaction due to insufficient care in its preparation but it must also provide the medication in labeled strength and quality. While the former may be readily observed in most instances, the latter may not be evident for some time, leading to a less efficient and slower recovery of the patient. When the cause is finally traced to the Pharmacy Department, it can but lessen the confidence of the medical and allied professions in the total operation of the department and incur loss of prestige to its personnel.

Need For Controls

It is obvious that strict controls during the preparation of parenteral injections as well as checks on the finished product should be an essential part of the sterile solution program. This paper will concern itself primarily with parenteral solutions, as the controls for surgical solutions and others remain the same except that pyrogen testing is deleted.

Controls should not be postponed until the product is completed but should be initiated with the first step of its manufacture. Precautionary measures have been stressed by many writers[2,3] but there has been a dearth of papers emphasizing the control procedures to be observed on the finished solutions. This lack of controls was revealed recently during a survey conducted on hospital prepared solutions.[4] Undoubtedly some of the material which is being presented is familiar to you, nevertheless, it has been included for the completeness of the discussion.

The subject may be divided into two sections, that is, firstly, controls that should be maintained during the preparation of sterile solutions and, secondly, controls on the finished product.

Controls During Preparation

Preliminary Measures. Mathematical errors can be avoided in calculations by keeping on file a master formula for the amount most commonly prepared. Quantities are governed by the amount being used currently and the equipment available. A copy of the formula is made on a manufacturing sheet and double-checked for accuracy. The lot number is assigned from a record of all manufactured products. The master manufacturing card should carry the following information:

1. Name of Product
2. Product Claim
3. Formula
4. Date of preparation and lot number of each batch.
5. Quantity Prepared
6. Staff Pharmacist in Charge

The current manufacturing sheet might follow a pattern similar to the one illustrated.

MANUFACTURING RECORD

Pharmacy Department
General Hospital

Product_____ Date_____
Claim_____ Lot No._____
Quantity Prepared_____

Formula:	Ingredients	Quantity	Checked

Prepared by _____ Checked by_____
Packaging: No._____ Size_____ Closures_____
No._____ Size_____
Label Directions: Name of Product_____
Quantity_____
Potency per unit volume_____
Lot No._____
Expiration Date_____

The type of balances used should be dictated by quantities being weighed. The balances should be checked periodically for accuracy. Graduates of proportionate sizes should be used to insure correct measurement.

Cleanliness. A suitable working area is an important consideration. An air-conditioned room with a minimum of traffic through the area is advisable. Special clothing, ultra-violet radiation, and easily cleaned walls and floors will aid in the maintenance of aseptic conditions. While costs may prevent the adoption of ideal conditions, a room that is easily cleaned and disinfected, free from drafts, with the elimination of unnecessary personnel from the working area, as well as the use of sterile caps and gowns provides a satisfactory replacement. To follow the above rec-

ommendations does not in itself assure an acceptable preparation. Nor does failure to follow them in detail eliminate the possibility of preparing a satisfactory product.

All equipment and containers should be meticulously clean. If possible, sterilization prior to use is an excellent safeguard. Pyrogens and micro-organisms can be destroyed by subjecting them to a temperature of 250° C. for one hour. Equipment should be cleaned immediately after use and rinsed with pyrogen-free water before using again. Hard glass as specified by the *United States Pharmacopeia* or Pyrex-glass containers are recommended to prevent solubility of glass during autoclaving and imparting alkalinity to the solutions. When new, bottles should be subjected to acid treatment, washed with hot detergent solution and rinsed with pyrogen-free water until no further traces of acid are present. A mechanical washer is a great time saver. The bottles should not show any water breaks after washing and should dry crystal clear. If bottles are not used within six hours, the washing procedure should be repeated.[5] Sintered glass Buchner funnels should be inspected each time for mechanical defects, absorption of medication, and adequate cleaning. Hard or lintless filter paper may be used if Buchner funnels are not available.

INGREDIENTS. Care must be taken that not only the required chemicals but the correct quantities are used. This is generally accomplished by having a pharmacist verify the ingredients and quantities and initial the manufacturing sheet. The procedure is an added precaution even when the operator is a pharmacist, but it is considered mandatory when a technician is employed.

The quality of the distilled water is dependent on the type of still, the method of maintenance and the efficiency of operation.[6] A well-baffled still where entrainment is impossible is required.[7] A schedule of cleaning the still should be made and measures taken that this is adhered to by the maintenance department. Steady and not too rapid heating prevents splashing and assists in producing water with low total solids. The use of a purity meter at the beginning and end of the distilling operation is advocated to determine in parts per million the total solids present as sodium chloride. Water below the U.S.P. limit of 20 parts per million does not eliminate pyrogens but, rather, there is less chance of pyrogens being present. In a report which appeared recently, distilled waters from 11 hospitals were studied.[8] All the samples were within the official tolerance limits for solids but three of these were found to be pyrogenic. Pyrogens can only be removed from solutions by charcoal and absorptive filters. The former is not a practical procedure as it is very difficult to remove fine particles of charcoal from solution. The use of two layers of Seitz serum number 3 filter pads (compressed asbestos) as recommended by Co Tui[9] slows down the preparation of large volume solutions. Thus, it is of utmost importance that freshly distilled water be used, as pyrogens can develop within several hours. This freshly distilled water should be stored in tanks specifically constructed to ensure complete drainage to prevent any possibility of bacterial growth and pyrogens.

Chemicals designated "chemically pure" do not in all cases denote drugs suitable for parenteral use. In many instances they may fall below the official requirement as the term "C.P" is dependent on the integrity of the manufacturer. It has been stated that commercial manufacturers use reagent grade chemicals to obtain the best possible quality.[10] In purchasing, the quantities ordered should be guided by the type of storage space available and the amount that is being used currently, in order to maintain the quality of the drugs. Improper storage has imparted pyrogenicity to dry non-pyrogenic substances.[11] As noted previously a temperature of 250° C. for a period of one hour, 170° C. for two hours, or treatment with acid-dichromate are required to destroy pyrogens. While the above temperatures could be used with inorganic substances, they would be unsuitable for the organic constituents. Similarly, autoclaving at 120°C. for four hours would cause the breakdown of the organic components and destroy only 98 percent of the pyrogens.[12]

Co Tui and co-workers[9] felt that while Seibert[7] and Rademaker[13] stressed the quality of the ingredients, especially the importance of having pyrogen-free water, they had neglected to emphasize the need to exercise every precaution to prevent contamination during the manufacture of solutions.

A permanent device to record the exhaust line temperature, the lowest in the autoclave, is a desirable feature. It must be remembered that only temperature sterilizes, while pressure is used to obtain the higher temperatures needed for sterilization.[14] Trial runs and periodic checks should be made to determine volume loss during autoclaving and an allowance should be made to compensate for this.

The correct label, well-attached and legible, is of primary importance. The lot number will give some indication at sight of the date of manufacture. Where shelf-life is limited, the expiration date should be included as well as any special storage conditions.

Controls on the Finished Products

FREEDOM FROM FOREIGN PARTICLES. This is the first test to be performed. The examination is carried out against white and black backgrounds using fluorescent light. Each container is examined for lint, floaters, etc.

In the manufacture of ampuls, a check for "leakers" is made by placing the ampuls in a solution containing a small quantity of dye and, when possible, heated. The ampuls are then examined for an influx of the color.

CHEMICAL ASSAY OF ACTIVE INGREDIENTS. The *United States Pharmacopeia XV* contains approximately 100 injections, 10 percent are large volume consisting primarily of electrolytes and/or dextrose. Their assay is a relatively simple procedure. Many of these assays are a part of the undergraduate curriculum in quantitative laboratory work. With the advent of the flame photometer, assays can be completed more rapidly than the official Volhard method for the assay of chlorides.[15] Another method, Fajan's,[16] gives a more rapidly observed end-point. Dichlorofluorescein is used as the indicator while titrating with silver nitrate. Dextrin is used to keep the precipitate in colloidal suspension for a sharper end-point. In this method dichlorofluorescein is used as an adsorption indicator. The white precipitate turns pink due to the adsorption of the silver ions on the particles of silver chloride at the equivalence point in the titration. Before equivalence point the solution contains an excess of chloride ions which are adsorbed by the precipitate giving it a negative charge. The organic ion is negatively charged and is adsorbed by the precipitate at the equivalence point, changing color.

There are relatively few hospitals that have a polarimeter for the determination of dextrose. Nevertheless, all hospitals do perform quantitative assays for blood glucose, generally using the Folin-Wu procedure. This same method can be used here. The solution being tested is diluted to the approximate values of the standard dextrose solutions employed. Dilutions should be carried out using volumetric pipettes and flasks.

The method consists of combining 2 ml. of the diluted dextrose solution with alkaline copper sulfate solution, heating in a water bath, cooling, adding the phosphomolybdic acid reagent and sufficient water to bring up to volume. The deep blue color is read in a colorimeter.[17]

STERILITY. The *U.S.P.*[15] stipulates that two media be used for this test, fluid thioglycollate and Sabouraud liquid media. They may be purchased in concentrated forms requiring only distilled water for reconstitution and are ready to be placed in tubes and sterilized. The thioglycollate medium* supports the growth of aerobic and anaerobic

organisms and Sabouraud* medium supports the growth of yeasts and molds.

For large volume solutions 40 ml. of the medium is placed in 25 x 200 mm. test tubes and sterilized at 121°C. at 15 pounds pressure for 30 minutes. While these media have been tested for growth-promoting and oxidation-reduction qualities, it is advisable to inoculate them with several pathogenic and non-pathogenic organisms. *Micrococcus pyrogenes* var. *aureus, Sarcina lutea, Escherichia coli* and *Clostridium sporogenes* may be used with the thioglycollate medium and *Candida albicans* for the Sabouraud medium and incubated under the specific conditions. Definite directions are given for testing solutions in small volumes to which bacteriostatic agents have been added.[15] The volume of the solution determines the amount of the inoculate.

The tests should be performed in a special room where aseptic conditions can be maintained. Ultraviolet light may be used to sterilize the area prior to conducting the test but not during inoculations. The solutions to be tested are wiped free of dust and swabbed with benzalkonium chloride solution (1:1,000). The closure of a diaphragm-type bottle should be wiped with 70 percent ethanol. Sterile air is admitted using sterile syringe with a sterile non-absorbent cotton plug in the barrel. A three inch, 19 gauge, hypodermic needle is suitable for withdrawing large volume solutions. The thioglycollate cultures are incubated at 34°C. and the Sabouraud at 22°-25°C. They are examined at 2, 4, 7 and 10 days. If at the end of the stipulated time no growth has appeared, the solutions are declared sterile. If growth has appeared, the solutions are recultured using double the number of samples. Samples for testing should be taken from different areas of the autoclave in order to be representative of the load. Control tubes of each medium should be incubated for sterility checks.

Pyrogen Test. Undoubtedly, proving the absence of pyrogens appears to be the most formidable test to the hospital pharmacist engaged in a sterile solution program. The test is based on the fact that when a pyrogenic solution is injected it precipitates a series of specific symptoms as aching in the lumbar region and limb joints, a feeling of cold, spasms of shivering, nausea and headache, followed by a rise in temperature.[18] While the *U.S.P. XV* has included about one hundred injections only some 25 percent require pyrogen testing and 10 of this number are in the large volume group. Dread of pyrogenic reactions can be dispelled by testing each batch of parenteral solutions prepared to make certain that they are beyond reproach.

Sterile solutions do not indicate freedom from pyrogens while non-sterile solutions may be apyrogenic. For example, Seibert[22] tested a solution so grossly contaminated that it was impossible to count the organisms but when the solution was injected into rabbits, it produced no fever.

Pyrogens are mucopolysaccharides of high molecular weight, 50 millimicrons to 1 micron in size, and are obtained from living sources.[9,20] They are filterable, heat stable bacterial by-products and they produce a febrile response on injection. There is some question as to the possibility of yeasts and molds producing pyrogens. During an investigation of hospital-prepared solutions by the writer, one of the solutions contained a mold contamination. After centrifugation, under aseptic conditions, an injection of the supernatant fluid did not produce a thermogenic response. Fever production can be reduced by dilution. Both the United States and British pharmacopeial tests are limit tests—the test does not indicate a complete absence of pyrogens but rather detects the maximum amount of pyrogen which when administered will just fail to cause a reaction in man. There is no standard dose which can be used for comparison.[21] There is no relationship between the pathogenicity of bacteria and their thermogenic potency[22] while the different types of pyrogens give varied responses.[20]

The mode of action of pyrogens has been described as a reduction in heat loss presumably due to constriction of the peripheral blood vessels rather than an increase in heat production. There is a time lag between injection and reaction, suggesting that it is not a direct effect upon the temperature regulating centers in the brain. It requires about 45 minutes and once started develops rapidly, the increase in temperature appearing in about 15 minutes. It has been reported that pyrogens added to both homologous plasma and normal saline before injection, showed a greater effect with the plasma.

The temperature response of the rabbit has been selected as the method of choice for pyrogen testing. Other methods such as the leucocyte response in rabbits have been investigated but have not been found as reliable.[23,24] Specific conditions have been designated for the test which include environmental requirements for the maintenance and the care of the animals. Variance in the temperature of the housing area may only differ by a plus or minus 3°C. Animals may be kept in separate quarters and brought into an

*B256-Fluid Thioglycollate Medium and B382-Sabouraud Liquid Medium are available from Difco Laboratories, Detroit, Michigan.

area of the same temperature and humidity for the test.

A brief outline of the test and a discussion of some particular points will give added data to those unfamiliar with some of the details. The routine described is one used in a study recently. Rectal thermometers were first tested for uniformity of temperature rise and length of time required to reach the maximum. While one minute appeared to be adequate, a two minute interval was selected. This period of time has also been recommended by others.[25] The thermometers were stored in benzalkonium chloride solution (1:1,000) to prevent spread of any possible infection.

Albino rabbits of both sexes were selected and allowed to become acclimatized for a few days, then weighed and their temperatures taken. Water was left in the cages at all times but food was withheld daily until noon. Thermometers were lubricated with petrolatum and inserted 7.5 cm. into the rectum for two minutes. The animals were held on the operator's lap and did not require any restraint.[26,27] A temperature card was set up for each animal to record its temperature ranges and a complete history of responses to testing. The rabbit was loosely wrapped in a towel and placed in an open rabbit box. The region of the marginal ear was shaved, swabbed with 70 percent ethanol and about 2 ml. of a known non-pyrogenic solution was injected to accustom the animal to the injections and to note if any temperature changes occurred due to the injection.

Following the initial injection, a sham test (*U.S.P. XV*) was performed within a few days. It consists of taking a series of four temperatures simulating the test but omitting the injection.

Syringes and needles used in the testing were washed thoroughly with a detergent, rinsed three times with tap water, rinsed twice with distilled water, and sterilized by heating at 250°C. for at least 30 minutes.

The day prior to the test five animals were selected for each solution to be tested. The rabbits were weighed, the initial temperatures were taken, and a second temperature was taken an hour later. The solutions to be tested were examined for foreign particles and a Solution Card was set up. A card listing all information pertaining to the solution and the results of all the tests was maintained for each solution.

On the day of the test the solution or solutions being tested were inoculated into the two media using aseptic technique. Immediately after the inoculations the solutions were placed into a water bath to bring the temperature to 37°C. The initial temperature of the animal was taken and the injection was made. This must be done within 30 minutes from the initial temperature recording. Three more temperature recordings were made at hourly intervals. The same procedure was carried out on two more animals. Two limitations with respect to temperatures are set by the *U.S.P.*—the rabbit must not have a temperature that exceeds 39.8°C. and the temperature differences among the animals are not to be more than 1°C. at the initial recording. At the end of the test the differences between the lowest and highest recordings are calculated to note if they are positive, negative, or doubtful. If doubtful, then the test must be repeated on five different animals. The character of the curve and the greater temperature variation from the negative response of the same rabbit will confirm the presence or absence of pyrogen.[28] Maximum temperature levels are reached two hours after a small dose, three hours after a large dose, and later for a massive dose. The height of the peak is a function of the dose.[29]

Some points that might be emphasized are as follows:

Animal weights. A lower limit of 1500 grams is recognized officially, for small animals are less sensitive to pyrogens. As the solution is injected on the basis of weight, 10 ml. per Kg., many workers limit weight to a maximum of 4 Kg.[29] To maintain this range it has been recommended that animals be kept on an 80 gram diet five days a week.

Degree of Restraint. The *Pharmacopeia* does not set any conditions but reports have appeared indicating that restraint raises rabbit temperatures.[30] In our work we found very little restraint was needed for either temperature taking or injection.

Injection. A sterile pyrogen-free 50 ml. syringe and a three-inch hypodermic needle were used to remove the solution from large volume containers. For the injection the needle was changed to one of one-half inch, 22 gauge. The solution was injected as rapidly as possible, the rate was limited only by the size of the needle. The rate of injection does not affect the temperature.[19]

Temperature variations. It is not unusual to find that the second temperature recording will show a drop from the initial. This has been observed by Kessler[27] as well as others. Unless the drop is marked, that is 1°C., it can be disregarded.

Animal tolerance. The *U.S.P.* sets no limit to the number of times that an animal may be used. Some workers have used an animal as many as fifty times with adequate responses.[23] There are some differences of opinion as to whether animals

develop tolerance or sensitivity, and as to the period of time that should elapse after a thermogenic response before the rabbit can be used again. The official requirement is two weeks after a febrile reaction. The animal must not be used more often than every 48 hours.

Stability

While sterility and freedom from pyrogens, once established, are no longer causes for concern, the maintenance of potency must be considered in terms of the future. This is especially important where new products are being introduced or a new dosage form is prepared. Temperature effects, the presence of air, the effect of light, *p*H, and autoclaving must be considered. Temperature changes may be observed by placing the product at refrigeration, room and higher incubation temperatures in the presence and absence of sunlight. Where the presence of air affects the stability of the preparation, provision should be made to use inert gases such as nitrogen or carbon dioxide.

Summary

Parenteral medications are a class of therapeutic and diagnostic agents which when prepared by approved techniques yield safe, sterile, non-pyrogenic products containing the labeled potency.

It is the pharmacist's responsibility to exert the greatest care in their preparation to avert severe reactions or even discomfort to the patient. It is the seriously ill patient who usually receives intravenous medication and a severe reaction may have disastrous results. Suggestions have been put forward stressing the need to institute a control laboratory as an extension of pharmacy services. Such self-discipline would ensure the hospital pharmacists of controlling their own destiny rather than having measures taken by outside groups.

The pharmacist who has applied controls throughout the preparation of parenteral fluids and on the finished product has discharged his professional and legal responsibilities and is assured of a feeling of satisfaction and confidence in his sterile solution program.

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TENTATIVE PROGRAM

Section on Hospital Pharmacy

Fourth Pan-American Congress

on Pharmacy and Biochemistry

Tentative plans for the Section on Hospital Pharmacy of the Pan-American Congress on Pharmacy and Biochemistry have been announced by Grover C. Bowles, Jr., Temporary Secretary of the Section. The Congress is scheduled for November 3 to 9 in Washington, D. C. with meetings being held at the Mayflower Hotel. The Section on Hospital Pharmacy will hold two sessions. The first is scheduled for 2:00 P.M. on Monday, November 4 while the second and final session will be held at 8:00 P.M. on Wednesday, November 6. A Temporary Chairman representing one of the countries other than the United States will be appointed prior to the meeting. A permanent chairman and a permanent Secretary for each of the Sections of the Congress will be elected at the Preparatory Session by a majority ballot of voting delegates of the Congress.

The following papers make up the tentative program for the Section on Hospital Pharmacy of the Pan-American Congress:

Monday, November 4

2:00 p.m.

1. Greetings
   LEO F. GODLEY, President of the American Society of Hospital Pharmacists and Director of Pharmacy Service, Bronson Methodist Hospital, Kalamazoo, Michigan.
   English
2. "Some significant Facets of the Audit of Pharmaceutical Service in Hospitals"
   DON E. FRANCKE, D.SC. and Clifton J. Latiolais
   Dr. Francke is the Program Director and Mr. Latiolais is the Assistant Director of the Audit of Pharmaceutical Service in Hospitals, Ann Arbor, Michigan.
   English
3. "Functions and Character of Social Pharmacy"
   GERONIMO ALFRED COGORNO, Guemes 4057, 50 Piso, Buenos Aires, Argentina.
   Spanish
4. "Needs For Hospital Pharmacists in the United States—1957 - Through 1970"
   GEORGE F. ARCHAMBAULT, Pharmacist Director and Chief, Pharmacy Branch, Division of Hospitals, U. S. Public Health Service, Department of Health, Education and Welfare, Washington, D. C.
   English
5. "The Feasibility of a Hospital Pharmacy to Prepare Disposal-Unit Injectable Medication for the Nursing Units"
   Ivan F. Bourn, M.Sc., HERBERT L. FLACK, M.Sc. and E. R. Browneller, M. D.
   Mr. Bourn is the Assistant Director of Pharmacy Service, Tacoma Indian Hospital, Tacoma, Washington. Mr. Mulsey is a member of the pharmacy staff, Jefferson Medical College Hospital, Mr. Flack is the Director of Pharmacy Service, Jefferson Medical College Hospital and Assistant Professor of Pharmacy, Philadelphia College of Pharmacy and Science and Dr. Browneller is the Acting Medical Director of Jefferson Medical College Hospital, Philadelphia, Pa.
   English
6. "Practical Suppository Formulations for Hospital Pharmacies" ROBERT E. LAWSON, Associate Chief Pharmacist, Springfield City Hospital, Springfield, Ohio.
   English
7. "Sterilization of Colloidal Oatmeal For Use as a Dusting Powder for Surgical Gloves"
   Albert M. White and LOUIS P. JEFFREY
   Mr. White is Instructor of Pharmacy, Albany College of Pharmacy and Mr. Jeffrey is the Pharmacist-in-Chief, Department of Pharmacy, Albany Hospital, Albany, New York.
   English
8. "Radio-Active Pharmaceuticals—A New Challenge to Hospital Pharmacists"
   CLIFTON J. LATIOLAIS, Assistant Director, Audit of Pharmaceutical Service in Hospitals, Ann Arbor, Michigan.
   English
9. "Utilizing Information Sources in Hospital Pharmacy Practice"
   GLORIA N. FRANCKE, Secretary of the American Society of Hospital Pharmacy, Ann Arbor, Michigan.
   English
10. "Hospital Pharmacy Service in Seguro Social of Costa Rica"
    LIC. RAFAEL ANGEL MONTERO G., Chief Pharmacist, Seguro Social Hospital, San Jose, Costa Rica.
    Spanish
11. "Hospital Pharmacy Representation in National Hospital Associations"
    JOSEPH A. ODDIS, Staff Assistant, Council on Professional Practice, American Hospital Association, Chicago, Illinois.
    English

Wednesday, November 6

8:00 p.m. Second and Final Session

12. "The Outpatient Pharmacy as a *in vivo* Prescription Laboratory For Pharmacy Students"
    Harold J. Hamilton, LOUISE POPE and William Heller, Ph.D. Mr. Hamilton is supervisor of the outpatient pharmacy and instructor of pharmacy, Miss Pope is the assistant chief pharmacist and instructor of pharmacy and Dr. Heller is Chief, Department of Pharmacy and assistant professor of pharmacy at the College of Pharmacy and the Medical Center, University of Arkansas, Little Rock, Arkansas.
    English
13. "Some Criteria For Establishing Minimum Standards for Pharmacy Practice in Hospitals"
    PAUL F. PARKER, Director, Division of Hospital Pharmacy, American Pharmaceutical Association, Washington, D. C.
14. Panel Discussion
    "Education and Training for Pharmacy Service in Hospitals"

Anyone wishing further details about the Congress may write to: George Griffenhagen, Executive Secretary, Fourth Pan-American Congress of Pharmacy and Biochemistry, c/o Smithsonian Institution, Washington 25, D. C.

The address of the Temporary Secretary is: Grover C. Bowles, Jr., Baptist Memorial Hospital, Memphis, Tennessee.

Enrollees at the **Chicago** *Institute take time out to pose on the steps of Burton-Judson Residence Halls where the Institute was held.*

Members of the **Seattle** *Institute gather on the steps in the center of the campus of the University of Washington.*

1957 INSTITUTES
on hospital pharmacy

by PAUL PARKER

NEARLY THREE HUNDRED HOSPITAL PHARMACISTS attended institutes during the summer of 1957. The enthusiasm exhibited at these meetings almost defies description. Though approximately 80 percent of the enrollees had never previously attended an institute, they met with a common interest. Getting acquainted was easy, and from the beginning the participants utilized every opportunity to discuss hospital pharmacy problems. From the time the first person arrived until the last certificate was presented, the conversations, the thoughts, the program and, indeed, the total atmosphere was permeated with some phase of hospital pharmacy. Attending an institute is a unique experience of constant professional contact which can only be fully appreciated by those who have participated.

The programs this year were broad in scope and covered subjects from "The Responsibility of the Hospital in Public Health" to a detailed description of the technique of taking the temperature of a rabbit in testing for pyrogens. Every attempt was made by the sponsoring organizations to present an interesting and informative program, and these organizations should be congratulated upon the extent to which this was achieved.

Catholic Hospital Association Institute

The Institute conducted by the Catholic Hospital Association, though considerably different from those conducted by the American Hospital Association was very effective. These programs have for several years been coordinated by the Executive Secretary of the C.H.A., Mr. Ray Kneifl, who is well known and appreciated by many hospital pharmacists. Due to illness, Mr. Kneifl was unable to attend the Institute this year. He was replaced by a relatively new member of the C.H.A. staff, Mr. John James, whose background experience is in hospital administration. Mr. James very capably became an integral figure among the hospital pharmacy group and his enthusiasm was obviously much appreciated. As during past years, the C.H.A. Institute was held in conjunction with the Association's Annual Convention which met in Cleveland during the latter part of May.

The key to the success of planning and conducting the C.H.A. Institutes lies with the Pharmacy Committee, which is composed of five Sisters—all practicing hospital pharmacists. Each serves a five-year term and one is replaced each year. Membership on this Committee represents five geographic regions of the United States and Canada, and the replacement each year is selected from the same region as the retiring member of the Committee. The Sister serving her fifth year becomes Chairman of the Committee. This is a unique system for perpetuating wide representation and still utilizing the advantages of experience. The 1957 Committee is pictured below with Mr. James and Norman Hammelman, from the V. A. Hospital in St. Louis, who also assisted with the Institute program.

Pharmacology Discussed

The entire morning and afternoon sessions of the first day were devoted to pharmacological

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Members of the **Catholic** *Hospital Association Pharmacy Committee (all Sisters) pose with the C.H.A. Institute Coordinators John James of the C.H.A. staff and Norman Hammelman, Chief Pharmacist, V.A. Hospital in St. Louis. Sisters are (top, left to right) Sister Marian, S.C., St. Elizabeth Hospital, Elizabeth, New Jersey; Sister Alberta, S.P., St. Vincent de Paul Hospital, Brockville, Ontario, Canada, and (bottom, left to right) Sister Cherubim, O.S.F., St. Joseph's Hospital, Joliet, Illinois; Sister Franciscana, O.S.F., Chairman, St. Joseph's Hospital, Memphis, Tennessee, and Sister Rebecca, O.S.B., Secretary, St. Benedicts Hospital, Ogden, Utah.*

discussions that would help the hospital pharmacist better interpret drug information to the other hospital professional staff. The discussions were led by Dr. Edward J. Ireland, Professor of Pharmacognosy and Pharmacology at Loyola University College of Pharmacy in New Orleans. A special luncheon was held at which tribute was paid to Mr. Kneifl, to the 1957 recipient of the H.A.K. Whitney Award, Sister Mary John, and to Mrs. Evlyn Gray Scott. The Sunday sessions opened with a discussion of the "Approval of Hospital Pharmacy Internships," by Paul F. Parker, Director of the Division of Hospital Pharmacy. This was followed by a discussion on "Accrediting Hospital Pharmacy Services," by Joseph A. Oddis, hospital pharmacist representative on the Council on Professional Practice of the American Hospital Association. Mrs. Evlyn Gray Scott, Chief Pharmacist at St. Luke's Hospital in Cleveland, demonstrated an actual meeting of the Pharmacy and Therapeutics Committee, with the assistance of the staff physicians from St. Luke's Hospital. At the afternoon session Dr. George F. Archambault, of the U. S. Public Health Service, discussed "Nonprofessional Personnel in the Pharmacy—Legal and Other Aspects." Norman Hammelman presented a paper on "Nonprofessional Functions and the Pharmacist." Mrs. Isabel Stauffer, Lecturer in Hospital Administration at the University of Toronto College of Pharmacy, discussed the subject of personnel planning.

A variety of subjects were presented on Monday, including "Administrative Problems," a panel moderated by Clifton J. Latiolais, Assistant Director of the Audit of Pharmaceutical Service in Hospitals. The "Substitution Problem" was discussed by Sister Mary Maurice from St. Joseph's Hospital, Augusta, Georgia, and the problems involved in "Handling Drug Samples," was presented by Sister M. Mariel from the St. Thomas Hospital in Akron, Ohio. Mr. Thomas Sisk, St. Joseph Hospital, Lorain, Ohio, presented the need for better "Inter-Departmental Relationships." The "Control of Investigational Drugs" was discussed by Dr. H. George DeKay, Professor of Pharmacy at Purdue University.

On the final day the following subjects were presented: "Cancer Treatment," "I.V. Therapy Trends," "Accidental Poisoning in Childhood," and "Disaster Planning in the Pharmacy." Dr. James L. Goddard, Chief, Accident Activities Bureau of State Services, U. S. Public Health Service, announced the formation of the National Clearing House for Poison Control Centers, and Mr. Thomas A. Foster, Chief, Civilian Health Requirements, Department of Health, Education and Welfare, urged the group to promote better organized methods of providing medical supplies during major disasters.

Seattle Institute

For the past three years the American Hospital Association has held two institutes on hospital pharmacy annually. A pattern has developed to hold one of these institutes each year at the University of Chicago, and the second institute is rotated in various other sections of the country. The setting for the institute this year on the campus of the University of Washington at Seattle was ideal. While the rest of the nation sweltered in the summer heat, the enrollees were at least occasionally concerned about the need for a topcoat. Seattle's climate, beautiful flowers, miles of coastline and congenial hospitality were all conducive to a most enjoyable Institute. The members of the Washington Society of Hospital Pharmacists were excellent hosts. A reception was held for the enrollees immediately after arrival, which provided an opportunity for everyone to become acquainted. The names Roberta Dodds (charming lady president of the Washington Society), Joe Birmingham (chief politician and "fixer-upper"), Cyrilla Jensen (boatride arranger), and George Gruber (chauffeur) will not soon be forgotten.

The program opened with greetings from the president of the University of Washington, Dr. Henry Schmitz. The subjects on the first day were of a general nature, including "The Expanding Responsibilities of the Hospital in Public Health," "Hospital Administration and Organization," "Expanding Responsibilities of the Pharmacist in the Hospital," and a full afternoon of lecture and demonstration on "Communications." Though broad in nature, these subjects set the theme for stimulating interest in hospital pharmacy during the remainder of the week.

Cruise on Puget Sound

On Monday evening the Washington State Hospital Pharmacist group coordinated a cruise to a beautiful secluded island on Puget Sound, where members of the Institute were introduced to clam nectar and barbecued salmon. After this refreshing outing, the enrollees were completely in the spirit of settling down to a week of work and professional discussions.

The "Organization of the Pharmacy and Therapeutics Committee" was discussed by a well-known former hospital pharmacist, Jerry Yalon, who is now Associate Director of the University of California Hospital in San Francisco. A highlight of the day was the demonstration of a

Pharmacy-Nursing Committee in action, which was moderated by Grover Bowles, Chief Pharmacist, Baptist Memorial Hospital in Memphis, with the cooperation of the nursing staff at Swedish Hospital in Seattle. Although Swedish Hospital did not have such a committee until that time, the demonstration was so convincing that it may well have served to actually organize such. Clifton Latiolais distributed a very complete list of information sources for hospital pharmacists during his presentation of "Utilization of Information Sources." (A limited number of copies of the material which he distributed is available from the Division of Hospital Pharmacy in Washington.)

The presentations by physicians at the Seattle Institute were particularly outstanding. Dr. J. Thomas Payne presented a paper on "Control of Hospital Infections," that well illustrated the quality of these presentations. Dr. Payne's paper has been submitted for publication in THE BULLETIN at a future date.

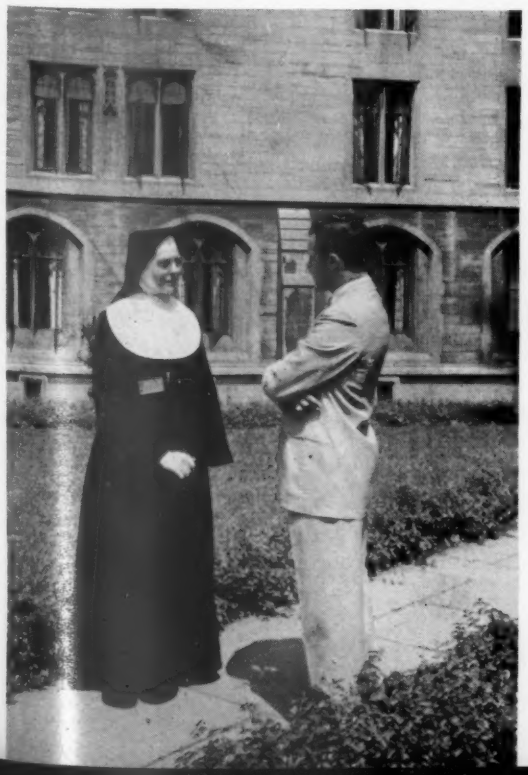
Everyone had a chance to "stump the experts" on Wednesday evening, when all members of the faculty served on a panel, which was moderated by President Leo Godley. Questions for discussion had been submitted throughout the week and as usual there was insufficient time to settle all hospital pharmacy problems.

Thursday's program centered on more specific phases of hospital pharmacy practice and featured a number of relatively newcomers to the hospital institute faculty group. Ted Taniguchi from the King County Hospital in Seattle discussed "Bulk Compounding in the Hospital Pharmacy," Jack Heard from the University of California Hospital in Los Angeles covered "Special Considerations in Labeling Problems," and Frank Hollister, Chief Pharmacist at the Good Samaritan Hospital in Portland, Oregon, presented "Hospital Pharmacy Records."

A highlight of the Institute was President Leo Godley's "rabbit show." Designed exclusively for television, but presented at institutes for lack of a sponsor, his "Controls and the Manufacture of Parenteral Solutions" dramatically demonstrates the ultimate technique in testing for pyrogens.

Though every institute leaves a desire for more, everything about the Seattle Institute was especially thus. Representation included Alaska, Saudi Arabia, and a goodly number from Canada—sufficiently broad to provide an experience in international relations.

Sister Alice, C.S.J., from St. Mary's Hospital in Minneapolis gets a pointer from Institute Coordinator, Joe Oddis as they meet in the Burton-Judson Court.



Frank Hollister (right), Chief Pharmacist, Good Samaritan Hospital, Portland, Oregon discusses his paper on "Hospital Pharmacy Records" with President Leo Godley (left) and the Executive Secretary of the Washington Hospital Association, John Bigelow (center).

One Clinic Session group at the Chicago Institute preferred to hold their daily sessions on the patio. Group leader is Charles Weiss from Akron General Hospital, Akron, Ohio.

Members of a Drug Charging panel at the Chicago Institute are (left to right) Louis Gdalman, Chief Pharmacist, St. Lukes-Presbyterian Hospitals, Chicago; Peter Solyom, Chief Pharmacist, University of Chicago Clinics; President Leo Godley; Hiram Sibley, American Hospital Association staff, and William Silverman, Associate Director, Michael Reese Hospital, Chicago.

Chicago Institute

By and large, the program of the Chicago Institute duplicated that in Seattle. However, no two institutes are exactly alike because the people who attend them are so much a part of determining its atmosphere. The hospitality of the Illinois Society of Hospital Pharmacists was also commendable. Everyone especially enjoyed the visit to Pete Solyom's Department at the University of Chicago Clinics. The "sleep, eat and meet" in the same building arrangement, which is made possible by the use of the Burton-Judson Courts at the University of Chicago, is certainly a convenience to "instituters."

Clinic Sessions

A unique feature of the institutes this year was the introduction of "clinic sessions" to replace the workshops of former institutes. All enrollees at both the Seattle and Chicago Institutes were divided into groups of approximately ten people who met for at least a half hour at the conclusion of each day's program. The groups informally evaluated the program for the day and discussed hospital pharmacy problems at the individual hospital level. The clinic session groups serve admirably to achieve a close acquaintance among pharmacists from comparable size hospitals, providing the basis for answering many of the individual problems. Group leaders were chosen from the enrollees and faculty members were barred admission except by invitation. Some remarkable new leadership talent was discovered. The clinic session leaders made a report to the Institute Coordinator each day and the reports served as an excellent critique for the entire program.

The American Hospital Association, the Catholic Hospital Association, the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, the Division of Hospital Pharmacy, the Washington State Hospital Association, the Washington State Society of Hospital Pharmacists, and the Illinois Society of Hospital Pharmacists have cooperated during 1957 to conduct three institutes of outstanding caliber. There surely must be a great deal of satisfaction among the officers, staffs, and members of these organizations for making these continuing education programs possible. At least every person attending the institutes appreciated their value, and wholeheartedly recommends them as a "must" for those practicing hospital pharmacists who have not attended an institute.

Left to right: Leo F. Godley, Mrs. Don Francke, Don Francke, J. E. Smith, Mrs. J. L. Summers, J. L. Summers, Mrs. Frank Zahalan, Frank Zahalan, Sister Mary Ancilla, J. Goldapple, Mrs. J. Goldapple, G. R. Paterson, Dean A. F. Larose, J. C. Cusson, Mrs. J. C. Cusson, and Mr. S. Boulkind.

Canadian Society Celebrates Tenth Anniversary

The Canadian Society of Hospital Pharmacists celebrated its Tenth Anniversary at its Annual Meeting held in Montreal on August 10 and 11, 1957. President Leo F. Godley and Secretary Gloria Francke represented the ASHP at this meeting. In bringing greetings from the ASHP, President Godley recalled the close spirit of friendly cooperation which has existed between the two North American Societies of Hospital Pharmacists and the similar, but nevertheless unique, problems which must be faced and solved by each group. President Godley pledged the continuing cooperation and interest of the ASHP to the officers and members of the Canadian Society of Hospital Pharmacists and felicitated them upon their ten years of progressive accomplishment.

The opening event for the Tenth Anniversary celebration was a dinner-dance, with entertainment which included singing of French folk songs. Mr. J. Goldapple of Montreal served as Chairman of the Planning Committee. Master of Ceremonies for the banquet was Mr. Frank Zahalan, President of the Quebec Branch of the C.S.H.P. and Chief Pharmacist at Montreal General Hospital. During the evening Sister M. Ancilla was honored for her long years of outstanding service as Editor of *The Hospital Pharmacist*, the official journal of the C.S.H.P.

The business meeting of the Canadian Society convened at 9:00 A.M. on Saturday morning, August 11 at the Montreal General Hospital. President Jack Summers opened the meeting and outlined the program for the day. The morning session was devoted to presentations of reports of committees, and other business matters.

"The History of the Canadian Society of Hospital Pharmacists," was the title of the principal paper of the afternoon program. This was presented by Sister M. Francis, a hospital pharmacist and former student at the Ontario College of Pharmacy, University of Toronto, Toronto.

Later in the afternoon, official delegates from each Branch of the Canadian Society of Hospital Pharmacists submitted reports of activities during the past year. This was followed by reports of several of the standing and special committees. One of the reports was a proposed "Minimum Standard for Pharmacy Internships in Hospitals," which is being developed as a cooperative project between the C.S.H.P. and the Canadian Conference of Pharmaceutical Faculties.

The Canadian Society of Hospital Pharmacists was also recognized by the Canadian Pharmaceutical Association at a luncheon during the Association's Convention commemorating its Fiftieth Anniversary. Here, contributions of hospital pharmacists to Canadian Pharmacy were cited and President Summers expressed appreciation to the parent group for their encouragement through the years.

At the close of the meeting, Mr. J. E. Smith of the Royal Jubilee Hospital in Victoria, British Columbia, was installed as president of the C.S.H.P. On accepting the presidency, Mr. Smith commented on the problems facing the Canadian Society and urged cooperation among the Branches throughout Canada.

a brief account of our trip to ROME and our audience with POPE PIUS XII

by SISTER MARY BERENICE, S.S.M.

IN MAY 6, 1957, Reverend Mother Concordia, Sister Mary Celeste and I left St. Louis on our trans-Atlantic flight to Rome where we expected to have the privilege of an audience with our Holy Father and to receive his personal blessing. It was 5 P.M. that same day when we left New York and were scheduled to stop one hour in Shannon, Ireland, one hour in Paris and to arrive in Rome at 4:45 the following afternoon, a flight of about sixteen hours.

As we left New York, one of the crew demonstrated the use of the life preservers, in the event that we should be forced to "ditch." Even though that was a routine procedure, I feared that if we should be forced to use it, most of us would not know what to do first. It was daylight for quite some time and as we watched the beautiful sight of the ocean below us and the sky above, it seemed that the Creator was shaping images of uncreated beings in the clouds, as forms of faces and creatures appeared and again disappeared back into their nothingness.

After a few hours someone began counting, one - two - three over the microphone and something in the tone of voice made one sense danger even before the announcement was made that there was trouble with the number one engine and that we should have to stop at Gander, Newfoundland in order to determine the extent of the trouble. At this point, Reverend Mother began praying the rosary aloud until we reached Gander at 12 midnight. Other passengers also prayed.

We waited in the terminal building until about 2:30 A.M. when we were told that we would be put up for the night, since the source of the difficulty had not yet been discovered. Everyone was grateful that at least we had reached Gander without any major disaster. It was not until noon the following day that a new plane arrived from New York and we were again on our way, and, as someone put it, there now was a new meaning for the letters T.W.A., i.e. "Try *W*once Again." On leaving Gander it was light for a long time, then it suddenly became dark without an intervening period of twilight. We reached Paris at midnight instead of at noon the previous day, and the airport of Rome at 4:45 A.M., just twelve hours later than our scheduled time.

Coming into Rome, we drove along one of the most famous highways of the world, the old Appian Way that extends from Rome to Lake Albano on the outskirts of Rome. It was with a feeling of awe and reverence that we passed along the way that Saints Peter and Paul and a multitude of early Christians traveled on their mission to spread the Gospel of Christ and, in many instances, to shed their blood for the Faith. There is a tradition that Christ, Himself, met St. Peter on this Appian Way, when the latter was fleeing Rome. The story has become familiar to nearly everyone since it so recently has been told in the picture "Quo Vadis"—I shall not repeat it here. However, along this way is a chapel called "Quo Vadis" and according to the same tradition it is on this spot that Christ met St. Peter. In the center of the little chapel is an area chained off, surrounding footprints impressed into the stone. It is told that these footprints are those of Christ as He met St. Peter on that very spot.

After a short drive we arrived at Salvator Mundi Hospital which was to be our home during our stay in Rome. The hospital, situated high on the Janiculum Hill, is a jewel among hospitals of Rome. Its beautiful surroundings are made even more beautiful by many exotic trees, shrubs and flowers. From the roof of the hospital there is a wonderful view of the Eternal City and its environs with mountains forming the skyline.

The four story hospital building has a capacity of about 100 beds and is quite modern. Although it is designated as an international hospital, there is almost an air of Americanism about it.

On our third day in Rome, the great day of our long-awaited private audience with our Holy Father became a reality. It is impossible to describe the impressions one experiences on such an occasion. We were privileged to visit with our Holy Father for a short time in his private office, then we returned to the adjoining room where the other members of our group awaited us, and where our group of nine persons was photographed with our Holy Father.

Rome has undergone many changes during the past nineteen years. The entire approach to St. Peter's Basilica from Castle Sant' Angelo has been improved. In 1938 there were two narrow streets leading up to the Piazza of St. Peter's from the Bridge of Sant' Angelo, but the houses along these streets have been demolished and one wide street made.

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Pope Pius XII is shown with Mother Concordia, Sister Mary Berenice (at the left of Pope Pius) and Sister Mary Celeste.

One also observes a certain modern trend in the customs of the people that were not apparent nineteen years ago. At that time automobiles were rarely seen on the streets. Today, the streets are crowded with all sorts of motored vehicles, and as it seems, with anything that will run. One sees a few large cars, but mostly tiny ones, three-wheeled conveyances, motor scooters, motorcycles, and the traditional bicycle, as well as one-horse carts which are still in operation. It is not uncommon to see a man on a motorcycle, a woman riding side-ways behind him with a child between them and an infant in the woman's arms. There also are many more sidewalk cafes. Frequently one sees large sides of meat and fowls hanging uncovered in the open air in front of shops that open directly on the streets.

Numerous relics of religious interest are found in many churches of Rome, *e.g.* the Church of the Holy Cross possesses the Latin Inscription which Pilate hung upon the Cross of Christ, a large piece of the Cross, itself, one of the Nails used in the crucifixion, and two of the thorns from our Divine Savior's Crown of Thorns. The Church of St. Praxedes possesses the Pillar to which Christ was bound during His scourging. The table of the Last Supper is preserved in the Church of St. John Lateran. I could go on and on in detailing the numerous relics of Christendom found in Rome, but that would make this short description too lengthy. There also are a multitude of historic relics in many parts of Rome.

In addition to our own private audience, we attended one special function in which the fortieth anniversary of our Holy Father's consecration as Bishop was commemorated, and also two very impressive public audiences. Someone in attendance with the Holy Father, who also is a personal friends of ours, told us that he estimated the crowd at St. Peter's to number about ten-thousand persons.

Every Wednesday there is such a public audience in St. Peter's in which the Holy Father speaks to the various groups of persons in their own language and later walks among the people so that those in front have the privilege of speaking with him. Everyone tries to get as close as possible, however, a number of places in the front are reserved for those for whom a special audience is arranged. We were fortunate in having these reserved places on all three occasions. Never before have so many people come to Rome to visit a Pope. The halls that were formerly used for audiences are not large enough to accommodate the large crowds who come from all parts of the world today just to see the Vicar of Christ and to receive his blessing. During our visit in Rome we petitioned a special blessing from the Holy Father for the members of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. Later this blessing will be sent to us in the form of a certificate.

Our two weeks stay in Rome passed all too quickly and only too soon were we winging our uneventful way back home. We stopped for an hour in Geneva, in Paris and in Iceland—the "Land of the Midnight Sun."

It was a wonderful and unforgettable experience and yet we are happy to be home again, happy that we are Americans, and happy, too, that we are Sisters of St. Mary.

therapeutic TRENDS

edited by WILLIAM JOHNSON

Compound 25398—An Intravenous Anesthetic Agent

Compound 25398 (1,methyl-5 allyl-5-[1 methyl-2 pentynyl] barbituric acid, sodium salt) is an oxygen barbiturate and has been used to provide anesthesia for surgery in 285 patients. In a comparison study using rats, mice, rabbits, monkeys and dogs; compound 25398 was found to be three times as potent; one-half as long in action; and much less likely to show accumulation than thiopentobarbital. No venous irritation or hemolysis was produced in any of these investigative studies. In the series of 285 patients the drug was administered in a 1.0 percent solution using the intermittent injection technique and also in a 0.1 percent solution by a continuous intravenous drip method. The induction was rapid and complete in all patients. This anesthetic agent was applied satisfactorily to the range of patients ordinarily considered to be candidates for intravenous barbiturate anesthesia. During the period of induction and maintenance of anesthesia and the recovery period, the patients were relatively free of any serious complications directly attributable to the drug. This study is reported by Stoelting in *Anesthesia and Analgesia* 36:49 (May-June) 1957. The material for this study was supplied by Eli Lilly Research Laboratories.

Neomycin—As A Cold Sterilizing Agent

The use of neomycin solution as a cold sterilizing agent for urological instruments is reported by Quilter in *J. Urol.* 77:769 (May) 1957. This investigator establishes his criteria for a cold sterilizing agent as follows: effective against a wide spectrum of bacteria; immediate availability of instrument without washing or rinsing; sterilizing agent must not make instrument slippery; and the sterilizing agent should be re-usable under certain conditions. Initial experiments were concerned with the use of neomycin in 0.1 percent solution in which instruments were soaked for at least 30 minutes prior to use. After six months use of this solution, cystoscopes were inoculated with *M. aureus* and the solution was found to be bactericidal with 30 minutes exposure. Later experience with a solution of 0.5 percent concentration indicates that a five month old solution of this concentration is bactericidal against *P. vulgaris* when instruments are inoculated and the exposure time is 10 minutes. No evidence of toxicity is reported nor is there any case in which there was any evidence of cross infection from one patient to another. Neomycin was supplied as Mycifradin sulfate by the Upjohn Co.

Dihydrocodeinone Resin Complex—A Long-Acting Antitussive

Dihydrocodeinone-phenyltoloxamine-resin-complex is an ion exchange resin containing dihydrocodeinone and an antihistamine. Preliminary studies in animals confirmed the sustained release of dihydrocodeinone from the dihydrocodeinone-resin complex. It was discovered that the addition of small amounts of certain antihistaminics potentiated the depth of cough suppression and when the antihistamine, phenyltoloxamine, was added as a sustained-release resin complex a true potentiation was obtained. Chan reports in *Am. J. Med. Sci.* 234:207 (August) 1957 that this preparation meets the need for an antitussive which predictably suppresses for an 8 to 12 hour period the hacking, nonproductive cough, yet does not completely abolish the natural protection of the cough mechanism. Suppression of the useless cough for 8 to 12 hours after administration of one dose of this material (equivalent to 5 mg. of dihydrocodeinone) was superior to results obtained with the same amount of the drug taken every 2 to 4 hours. No side effects were observed. Tussionex is the trade name of R. J. Strasenburgh's dihydrocodeinone-phenyltoloxamine-resin complex.

Chlorothiazide—A Non Mercurial Diuretic Agent

Chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide) is an effective orally administered diuretic agent which is a nonmercurial and apparently is not toxic. It is a potent inhibitor of the renal tubular reabsorption

of sodium. It causes a minimal increase in excretion of bicarbonate and a considerable increase in excretion of chloride. An oral dose has a rapid onset of action (2 hours) and a short duration (12 hours) of effect and in current trials it maintained its effectiveness when administered daily. The maximum effect appears to be achieved at a dose of 2000 mg. daily (1000 mg. at breakfast and supper). No toxicity was observed in 20 patients who received the drug daily for 3 months. A dose of 2000 mg. given orally in two divided doses appears to be nearly as "potent" as 2 ml. of Meralluride. The result of this study by Moyer, Ford, and Spurr is presented in *Proc. S. Exp. Biol. Med.* 95:529 (July) 1957. Chlorothiazide was supplied for this study as Diuril by Merck Sharp & Dohme.

Compound 1943—An Antibiotic

An unidentified *Streptomyces* isolated from soil in Puerto Rico was found inhibitory to a variety of organisms on an agar streak plate. When grown under submerged aerobic conditions, the broth exhibited similar inhibitory ability, as shown in serial dilution assay. A crystalline antibiotic isolated from broth cultures of the organism has been given the designation 1943. Murray *et al* describe the antibiotic in *Antibiotics and Chemotherapy* 7:345 (July) 1957 and have studied *in vivo* and *in vitro* activity of this antibiotic. Ototoxicity is demonstrated in the form of vestibular disturbances in the cat. It is suggested that this property may be linked with the presence of guanidine groupings in the structure and that new antibiotics containing guanidine groups should be tested in cats at an early stage of development.

Propoxycaine—A Local Anesthetic Agent

Propoxycaine hydrochloride is diethylaminoethyl-2-propoxy-4-aminobenzoate and has been found to have ten times the activity of procaine when assayed by the guinea pig sciatic nerve test. Over a period of nine months propoxycaine hydrochloride was used as the local anesthetic in 71 surgical procedures. The patients were from a large industrial practice, and consequently most of the procedures involved the repair of crushing injuries, lacerations and amputations. The results of this series are published in *Am. J. Surg.* 94:111 (July) 1957. Salient features of the satisfactory performance of propoxycaine hydrochloride include rapid onset, effective in small dosage, prolonged anesthesia, and absence of side effects. Blockain is the George A. Breon & Co. trade name for propoxycaine.

Methindethyrium And Ethiquinium—Hypotensive Agents

Compounds IN 391 (methindethyrium) and IN 292 (ethiquinium) are asymetrical bisquaternary ammonium compounds that are moderately efficacious in lowering the blood pressure in hypertensive patients. In addition to central action observed in the laboratory, these drugs have properties when used clinically that indicate some degree of ganglionic blockade. Both compounds produce fewer side effects and have less antihypertensive effect than other ganglionic blocking agents, such as mecamylamine and chlorisondamine. These experimental preparations, IN 391 and IN 292, are indicated primarily for the treatment of patients with mild degrees of hypertension. This work was published in *Antibiot. Med. and Clin. Therap.* 4:445 (August) 1957. Both of these drugs were supplied by Irwin Neisler & Co. and the trade name for methindethyrium is Isotensen.

Fluothane—An Anesthetic Agent

A series of 310 cases is presented by Chang *et al* in which fluothane has been used as an anesthetic agent. It was administered using both the closed and semi-closed techniques. Fluothane (CF_3C-HC1Br) is a clear, colorless liquid with a rather pleasant odor. It has a specific gravity of 1.86 at 20°C. and a boiling point of 50.2° C. When exposed to light, fluothane decomposes slowly, forming volatile acids. This can be prevented by storing it in amber colored bottles or by adding thymol 0.01 percent W/W. Fluothane is noninflammable, non-explosive and it is stable in the presence of soda lime.

The chief advantages and disadvantages of this anesthetic agent are noted in a study appearing in *Can. Anaes. Soc. J.* 4:187 (July) 1957. Fluothane was supplied by Ayerst, McKenna, & Harrison Ltd., Montreal.

Xylopropamine—Analgesic Properties

A sympathomimetic drug, xylopropamine sulfate (1-(3,4-di-methylphenyl)-2-aminopropane), has been found to be capable of elevating the threshold of human subjects to experimentally induced pain. The method employed was electrical stimulation of the tooth pulp. In *Proc. Soc. Exp. Biol. Med.* 95:212 (June) 1957, Harris and Worley describe the experiment in which eight subjects were used under "double blind" discipline. Five and 10 mg. oral doses of xylopropamine were compared with a placebo and a "dry run." Tables are used to summarize the results of this experiment. Xylopropamine for this study was supplied by Hoffmann-La Roche, Inc.

timely drugs

Achromycin V

. . . combining the well-known antibiotic tetracycline with sodium metaphosphate to provide greater and more rapid absorption of tetracycline in the intestinal tract, is now marketed by Lederle Laboratories. The increased absorption of this compound is evidenced by higher and more rapidly attainable blood levels and by the excretion of the antibiotic in the urine. The average oral dose is 12.5 to 20 mg. per kilogram of body weight for adults and children. Each 0.25 Gm. capsule of Achromycin V contains tetracycline equivalent to tetracycline hydrochloride 0.25 Gm. and sodium metaphosphate 0.38 Gm., and is packaged in bottles of 16 and 100 capsules.

Achromycin V pediatric drops contain in each ml.: tetracycline equivalent to tetracycline hydrochloride 100 mg.; sodium metaphosphate 152 mg.; methylparaben 0.12 percent; and propylparaben 0.03 percent. The usual dosage of the drops is 5 mg. (1 ml.) per pound of body weight per day, and may be administered as drops or with small amounts of milk, water or fruit juices. The drops are packaged in 10 ml. plastic dropper-type bottles.

Achromycin V syrup contains in each teaspoonful of 5 ml., tetracycline hydrochloride activity 125 mg., and methylparaben, propylparaben and sodium bisulfite as preservatives. The syrup is available in bottles of 2 and 16 fluidounces.

Albamycin Sterile

. . . for intramuscular or intravenous use, is now available from the Upjohn Co. The drug is rapidly effective against a wide range of clinical strains of Staphylococci including strains resistant to other antibiotics and certain strains of *Proteus vulgaris*. Very high therapeutically effective blood concentrations are maintained for at least 12 hours after administration of parenteral Albamycin (novobiocin, Upjohn). It diffuses well into all body fluids and tissues except spinal fluid, and urinary excretion of the active antibiotic is sufficiently high to effectively treat urinary tract infections.

For adults the dosage of parenteral Albamycin is 500 mg. administered intramuscularly or intravenously every 12 hours. Children should receive 15 to 30 mg. per kilogram of body weight, depending upon the severity of the infection, at 12-hour intervals. The drug is packaged in the new Mix-O-Vial containing 500 mg. of the sodium salt with 175 mg. of nicotinamide. One compartment of the vial contains the Albamycin and nicotinamide; the other provides, as diluent, sufficient sterile solution of N, N-dimethylacetamide 10 percent with benzyl alcohol 0.9 percent to give a total volume of 5 ml. when mixed. Directions for using the Mix-O-Vial are given in the package.

Cees

. . . a cough syrup which quickly releases potent medication directly into the blood stream, is now offered by Norwich Pharmacal Co. Cees with GW-3 helps reduce allergic congestion with its resulting post-nasal drip which causes coughs and spreads bacteria. It helps clear congested bronchial passages where viruses and bacteria breed and are spread by coughing. The adult dosage is one teaspoonful up to six times daily at three to four hour intervals. The dose for children 6 to 15 years of age is one-half teaspoonful. Cees should not be given to children under 6 years except as directed by a physician. It is supplied in bottles of three fluidounces.

Darvon

. . . a non-narcotic pain reliever, has been marketed by Eli Lilly & Co. Extensive studies have shown that in relieving pain it is equivalent to codeine both in duration and intensity of action. However, it is not classified as a narcotic and in clinically useful doses does not produce euphoria, tolerance, or physical dependence. Darvon (dextro propoxyphene hydrochloride, Lilly), a synthetic chemical, is orally effective, may be administered with antipyretic analgesics such as aspirin, is compatible with many other medications without the occurrence of unexpected responses, and has caused no demonstrable toxic effects on the blood, brain, liver, kidneys or other body organs. It is of particular value for pain associated with recurrent or chronic disease. The usual adult dose is 32 mg. every four hours or 65 mg. every six hours as needed for pain. The usual adult dose for Darvon Compound is one or two capsules every six hours. The drug is supplied as 32 and 65 mg. capsules in bottles of 100 capsules. It is also available as Darvon Compound containing Darvon 32 mg., acetophenetidin 162 mg., aspirin 227 mg., and caffeine 32.4 mg. The Compound is packaged in bottles of 100 capsules also.

Furadantin Intravenous

. . . for refractory bacterial infections such as bacteremia, peritonitis, pneumonia and abscesses, when caused by Furadantin-sensitive organisms, has recently been announced by Eaton Laboratories. It may also be effective for genitourinary tract infections when the patient cannot take oral medication. The single dose of Furadantin (nitrofurantoin, Eaton) for the average adult is 180 mg., or 30 ml. (three ampuls) in at least 500 ml. of diluent. The recommended dilu-

ent is five percent dextrose. Although it is compatible with normal saline and 1/6 molar sodium lactate solutions, these should be used only when definitely indicated because of the possibility of further upsetting an already disturbed electrolyte balance. The intravenous solution is administered at the usual rate. The drug is supplied in 10 ml. ampuls containing 60 mg. of Furadantin each.

Imferon

. . . an intramuscular iron-dextran complex, is now available from Lakeside Laboratories. It is an isotonic, well-tolerated solution of iron-dextran complex providing the equivalent of 50 mg. of elemental iron in each ml. It is indicated where there is a definite need for parenteral iron in patients with iron deficiency anemia with (1) intolerance to oral iron; (2) gastrointestinal disease which may be adversely affected by oral iron, such as regional enteritis, ulcerative colitis, and gastric ulcer; (3) poor absorption of iron; (4) resistance to oral iron; or (5) depletion of iron stores when oral iron is ineffective in rebuilding iron stores. After calculating the patient's total iron need, the suggested dosage of Imferon is 1 ml. the first day, followed by 2 ml. daily or every other day, until the total required amount is given. In normal or fat people, up to 5 ml. daily may be given. Children over 20 pounds and small adults should receive no more than 2 ml. daily. Children between 8 pounds and 20 pounds should receive 1 ml. daily, and children under 8 pounds, 0.5 ml. daily. Imferon is available as 2 ml. ampuls in boxes of 4 and 24, and as 5 ml. ampuls in boxes of 4. Each ml. contains 50 mg. of elemental iron.

Milpath

. . . Wallace Laboratories, New Brunswick, N. J. has now combined Miltown with tridihexethyl iodide, an anticholinergic. The two drugs work together for a new approach in the treatment of gastrointestinal disorders. The new compound is known as Milpath.

Milpath is a tablet which contains 400 mg. of Miltown and 25 mg. of the anticholinergic tridihexethyl iodide. It is designed for a two-level treatment of gastrointestinal disorders such as gastric and duodenal ulcers, spastic and irritable colon, esophageal spasm, intestinal colic and anxiety neuroses with vague gastrointestinal symptoms.

The Miltown component of Milpath, unlike the barbiturates, tranquilizes the patient's anxiety and tension without the dulling effect which those sedatives often have. The other component, tridihexethyl iodide, is a clinically proven anticholinergic with low toxicity and few side effects. This drug works directly on the digestive tract to control damaging hypersecretion and hypermotility. In this way it relieves ulcer pain and promotes healing.

Norlutin

. . . a purified crystalline compound which provides orally potent progestational action, has been announced by Parke, Davis and Company. It is indicated in therapy for a variety of gynecologic conditions associated with pregnancy and menstruation, such as amenorrhea, menstrual irregularity, functional uterine bleeding, infertility, habitual abortion, threatened abortion, premenstrual tension, and dysmenorrhea. Clinically important side effects have not been a problem with the use of Norlutin.

Norlutin (norethindrone, Parke, Davis) is administered in varying dosages, depending upon the condition being treated. It is supplied as a 5 mg. tablet in bottles of 30 tablets.

Peganone

. . . a new anticonvulsant of the hydantoin series (3-ethyl-5-phenylhydantoin) now available from Abbott Laboratories, is especially effective in grand mal. It may be effective to a lesser extent in psychomotor seizures, and in some cases of petit mal and petit mal variants. It is notably lacking in side effects, such as gum hypertrophy, which are usually associated with hydantoin therapy. The average adult dose of Peganone (ethotoin, Abbott) is 2 to 3 Gm. daily, given after food in 4 to 6 evenly spaced doses. With patients on other medication, the dose of other drugs should be gradually reduced, while increasing the dose of Peganone, until optimal dose of each is achieved. Peganone is supplied as 0.25 Gm. and 0.5 Gm. tablets in bottles of 100 and 1,000.

Peri-Colace

. . . combining a fecal softener and a peristaltic stimulant, has been announced by Mead Johnson. It is indicated in constipation associated with impaired bowel motility. Colace (dioctyl sodium sulfosuccinate, Mead Johnson) reduces surface tension of intestinal water to form soft stools. Peristim, a standardized preparation of anthraquinone derivatives from cascara sagrada, stimulates peristalsis. Nausea, griping, and constipation rebound are minimized with this combination. Each capsule contains 100 mg. Colace and 30 mg. Peristim. Each tablespoonful of the syrup contains 60 mg. Colace and 30 mg. Peristim. For adults and older children the dosage is usually one capsule or one tablespoonful of the syrup at bedtime. The capsules are available in bottles of 30 and 60; the syrup is packaged in eight ounce bottles.

Rabies Vaccine (Duck Embryo)

. . . for the prevention of rabies in exposed subjects, has been released by Eli Lilly & Co. This vaccine is a suspension of embryonic duck tissue infected with fixed virus, to which beta-propiolactone has been added as a virucidal agent. Local reactions to the injected material have been observed to be somewhat less than those seen with vaccines of brain origin. The complete treatment consists in one subcutaneous dose daily for 14 days. It is recommended that the injections be made subcutaneously under the skin of the abdomen in alternate sides each day. One dose of vaccine is contained in an individual vial accompanied by one ampul of Water for Injection U.S.P. The contents of the ampul of Water for Injection are withdrawn into a heat-sterilized syringe, injected into the vaccine vial, and gently mixed. A 23 or 24 gauge needle, approximately ½ to ¾ inch long, is recommended. The vaccine is supplied in a package containing seven doses of dry vaccine with seven ampuls of Water for Injection. This is not a complete treatment for any type of rabies exposure since the treatment must consist of 14 daily doses.

Notes and Suggestions

by CLIFTON J. LATIOLAIS

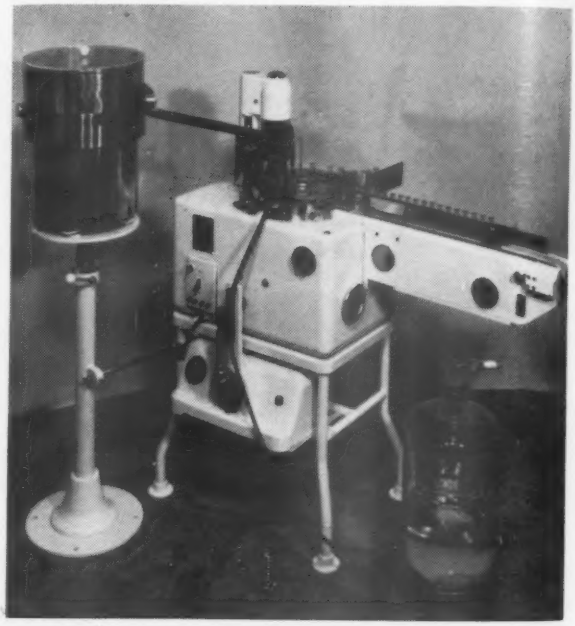
BOTTLE SEALING MACHINE

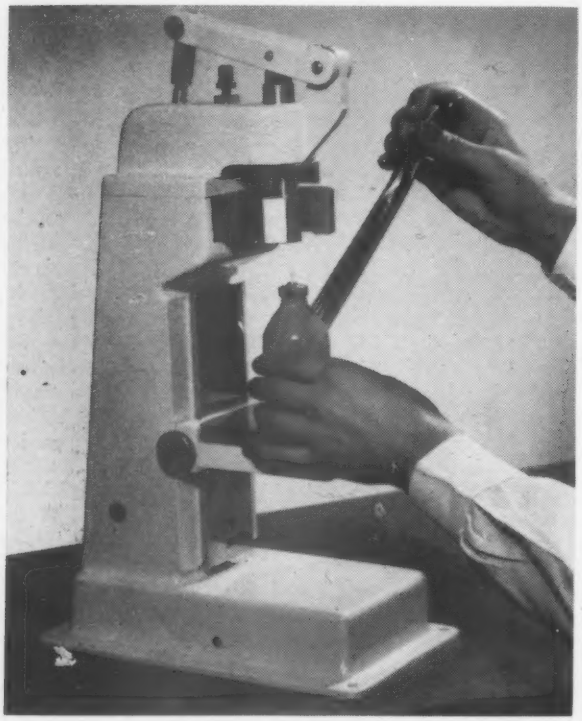
The Capsolut Sealing Machine, Model Universal*, is well suited for sealing small or large quantities of containers of injection preparations and other sterile solutions, as well as tablets, capsules, etc. and also for sealing aerosol bottles and vials with pipettes (dropper bottles for collyria, etc.).

This sealing machine can accommodate bottles from 40 mm. to 240 mm. high and from 8 mm. to 100 mm. high. The sealing mechanism can accommodate seals from 8 mm. to 45 mm. in diameter. Sealing mechanisms are easily interchangeable. The size of the unit is 16 cm. wide, 28 cm. deep and 48 cm. high and weighs 16 Kg.

A fully automatic sealer, Type A-3 is available for use in large batch operations.

*Arenco Manchine Company, 25 West 43rd Street, New York 36, New York





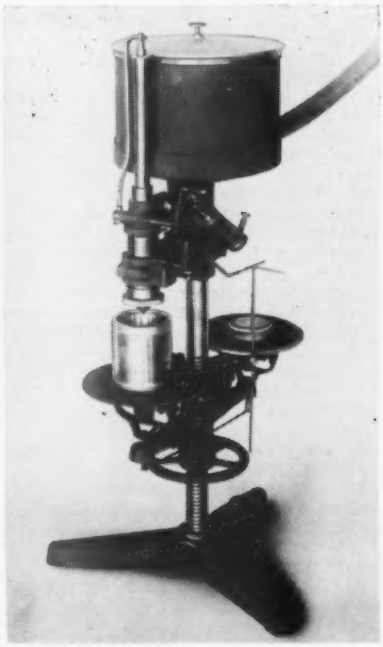
Lower right photo shows Capsolut Sealing Machine in process of sealing vial; upper right photo shows Type A-3 machine for large batch operations; and lower right photo shows application of machine in sealing dropper vials.

MARKING AND PRINTING MACHINES

An illustrated brochure describing Rejafix marking and printing machines has been issued by Popper and Sons, Inc., 300 Fourth Avenue, New York 10, New York. These machines are available in hand operated, semi-automatic and fully automatic units.

MONOSCALE SEMI-AUTOMATIC FILLING MACHINE

The Kiefer Monoscale Semi-Automatic Machine* fills by accurate balanced measure, without spatter, drip or overflow. The containers are placed on a tray under the spout, a little lever opens the valve, and when the exact amount is deposited, the scale balances, automatically stopping the flow. The Monoscale handles up to a 5



gallon size container, with quick adjustments when changing from one size container to another. All metal parts in contact with the product can be supplied in types 303, 304 or 316 stainless steel.

*Karl Kiefer Machine Company, Cincinnati 2, Ohio

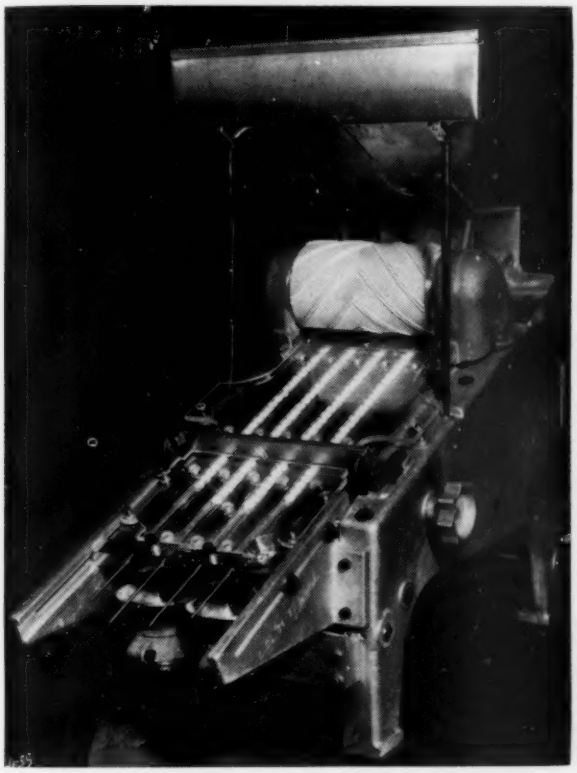
COSMETICS MANUALS

The Atlas Powder Company, Wilmington 99, Delaware has recently issued two booklets on cosmetic formulations. One booklet (33 pages) is called "The Guide" which describes various Atlas surface active agents, an HLB system of surfactant selection and suggestions for formulating cosmetic emulsions.

The other manual (32 pages) is called "The Formulary" which includes typical cosmetic formulations of the oil-in-water and water-in-oil type emulsions, and non-emulsified cosmetics.

TABLET AND CAPSULE COUNTER

The Sampler Tablet and Capsule Counter* is a small table model machine for filling low count packages at 20 to 40 per minute or for larger quantity packages at slower speeds. The white rubber feed roll rotates slowly against the direction of tablet flow and is adjusted to permit only one layer of tablets or capsules to flow down the plate. The machine does not vibrate. The correct count is carried on the drop gate. When a foot switch is pressed the gate drops the tablets into the bottle nozzles which are vibrated during the filling cycle to prevent clogging of tablets in bottle neck. The operator handles two bottles at a time. There are four feed tracks, each track adjustable for tablets from ¼" to 9/16" and for capsules from size 5 to 00. Count is changed quickly by setting four count pins.



Dimensions of the counter are 15" wide by 27" deep by 27" high. All metallic contact parts are stainless steel and chrome plate. Equipped with 1/20 H.P. motor 110V. Hopper holds 35,000 five grain aspirin tablets. Current price is $1,200 FOB, Fitchburg, Massachusetts.

*Lasko Company, Inc., P.O. Box 257, Fitchburg, Massachusetts

selected pharmaceutical abstracts

and summaries of other articles interesting to hospital pharmacists

edited by LEO F. GODLEY *and* CLIFTON J. LATIOLAIS

TOXICITY OF ETHANOLAMINES

Ethanolamines in Topical Preparations, Draize, J. H. et al, Drug and Cos. Ind. 81:40 (July) 1957.

An investigation was made to demonstrate the toxic effects, if any, of the ethanolamines, when incorporated in cosmetic and topical drug preparations.

The subacute dermal toxicity of mono-, di-, and tri-ethanolamine was studied using rabbits as the test animal. These compounds were tested topically as free amines in various concentrations in aqueous solution and ointment bases and also administered orally.

From the data presented the authors indicated that a very low order of dermal toxicity exists for the ethanolamines when employed at concentrations up to 5% in aqueous media and U.S.P. hydrophilic and white ointment bases. Monoethanolamine was found to be slightly more irritating than the other amines studied. Monoethanolamine was found to be considerably more toxic than triethanolamine when administered orally.

EDWARD SUPERSTINE

STERILIZATION, ELECTRON

Present Status of Sterilization by High-Speed Electrons, Ranftl, J. W., Bull. Parenteral Drug. Assoc. 2:24 (March-April) 1957.

Sterilization by ionizing rays has aroused considerable interest in the food and drug industries mainly because it is a relatively heatless process. Currently, most radiation sources for sterilization are machines which emit high energy electrons. These machines are capable of producing the radiation dosage of 2,000,000 rep needed to sterilize most products. One rep is defined as the absorption of 93 ergs of energy per gram of material.

Pharmaceuticals which have been sterilized by radiation include antibiotics, multivitamins, hormones, and protein materials. During the sterilization of some of these drugs, side effects of color and potency change occur. Also, undesirable products may be produced by the radiation. However, such changes may often be overcome by changing the drug itself, changing processing conditions, or by adding materials to absorb the adverse effects of the radiation.

At the present time sterilization by radiation is costly and limited to large scale operations. However, in the future facilities for cooperative sterilization centers may become available.

JOHN D. LUCASSE

STERILIZING OILS FOR INJECTION

The Sterilization of Oils for Injection, Bandelin, F. J. and Tuschoff, J. V., Bull. Parenteral Drug Assoc. 2:16 (May-June) 1957.

The bactericidal activity of 30 different compounds, all active to some degree in aqueous solution, was investigated when these compounds were dissolved in sesame oil. Experimentally the compounds were tested using separate suspensions of spores of *B. subtilis* and *Cl. tetani* and viable cells of *Strep. fecalis* and *E. coli* in sesame oil. At room temperature and at elevated temperatures of rising increments, rapid antibacterial action was attained in only a few instances. Phenylmercuric benzoate, 8-hydroxy-quinoline benzoate, benzyl alcohol, various alkyl-substituted cresols and halogenated phenols showed various degrees of activity. Phenol and chlorobutanol gave poor results. Of all compounds tested only phenylmercuric benzoate killed all organisms in two hours at 0.1% concentration. It was apparent that some compounds exerted a selective action against certain bacteria. Therefore, the authors suggest the advisability of investigating the activity of combinations of these compounds.

JOHN D. LUCASSE

STABILITY OF N.F. ANTISEPTIC SOLUTION

A Study of the Stability of N.F. Antiseptic Solution, King, Louis D. and Doerrer, Richard C., Drug Standards 25:112 (July-Aug.) 1957.

The original formula for official Antiseptic Solution, which appeared in the U.S.P. VIII in 1905, has been revised four times since it was deleted from the U.S.P. beginning with the N.F. IV formula in 1916. Yet it continues to draw a number of criticisms. Those included in the article were as follows: (1) it is stinging to the oral mucosa; (2) extemporaneous preparation is both difficult and lengthy; (3) it is not germicidal; and (4) the process of filtration, as described in the present N.F. method of preparation, not only removes many of the active ingredients but also creates an unstable product.

For these reasons King and Doerrer undertook an investigation directed toward improving the stabilization, antibacterial activity and esthetic qualities of the final product through correction of the formula.

It was found that the addition of 15% propylene glycol to the official solution gave a clear and stable product. The use of propylene glycol as a solubilizing agent also intensified the flavor and enhanced the esthetic qualities of the final preparation. Preliminary investigation showed that the use of iodothymol in place of chlorothymol produced an approximate five-fold increase in the antibacterial activity. And finally, that the inclusion of four flavoring ingredients does not seem to be necessary—it being found that methyl salicylate in proper amount most nearly simulated the official product.

King and Doerrer have suggested that the National Formulary consider the following: (1) the addition of 15 percent propylene glycol to the present formula; or (2) continue investigation of the following formula: Boric Acid 25.0 Gm.; Iodothymol 0.5 Gm.; Methyl salicylate 0.5 ml.; Alcohol 300.0 ml.; Purified water, q.s. ad 1000.0.

THEODORE J. BENYA

BINDING AGENT FOR COMPRESSED TABLETS

Veegum as a Binding Agent for Compressed Tablets, Patel, R. P. and Rana, A. S., Indian J. of Pharm. 19:4 (Jan.) 1957.

The binding properties of Veegum (complex colloidal aluminum magnesium silicate) were compared with those of starch paste, mucilage of acacia and syrup in the preparation of compressed tablets containing soluble and insoluble medicaments.

Tablets containing sodium bicarbonate and lactose as soluble medicinal agents and calcium carbonate and kaolin as insoluble medicaments were prepared using Veegum dispersion 10%, starch paste 10%, acacia mucilage 20%, and syrup 50% as binding agents. Starch 10% and talc 2% were used as disintegrating agent and lubricant respectively in all the investigations.

The study showed that the tablets prepared with Veegum as binding agent disintegrate more rapidly than those prepared with the other binding agents, although they have identical hardness and compression ratio. Tablets prepared with Veegum meet the requirements for compressed tablets mentioned in the *Indian Pharmacopoeia* and the *British Pharmacopoeia.*

CLIFTON J. LATIOLAIS

TETRACYCLINES, SOLUBILITY AND COMPLEXING PROPERTIES

The Solubility and Complexing Properties of Oxytetracycline and Tetracycline I. Interaction in Aqueous Solution, Gans, E. H. and Higuchi, T., J. Am. Pharm. Assoc. Sci. Ed. 46:458 (Aug.) 1957.

The strong acidic polarity of oxytetracycline dihydrate and tetracycline trihydrate form soluble complexes in aqueous solutions with agents possessing strong electronegative centers. The solubilizing activity of the hydrotropic compounds used is roughly in the following order: Sodium salicylate, sodium parahydroxy benzoate, sodium saccharin, sodium p-aminobenzoate, caffeine, and N-methyl pyrrolidone. In all cases the tetracycline interactions are greater than those with oxytetracycline. The experimental and analytical procedures are described.

NORMAN HO

EFFECT OF FLAVORS ON PENICILLIN STABILITY

Effect of Flavors Upon the Stability of Penicillin in Oral Penicillin-Triple Sulfonamide Powders, Charnicki, W. F. and Kober, M. L., J. Am. Pharm. Assoc. Sci. Ed. 46:481 (Aug.) 1957.

Thirty-four flavors were screened for their ability to mask the bitterness of an oral penicillin-triple sulfonamide powder mixture, which when diluted with water to yield a 5 ml. of suspension contains 100,000 to 250,000 units of potassium penicillin G and a mixture of sulfamerazine, sulfadiazine, and sulfamethazine totaling 0.5 Gm. Those formulations selected underwent accelerated and long-term stability studies for penicillin-flavor reactions. Clove and anise oils caused little decomposition of the penicillin whereas vanillin and coumarin caused practically complete inactivation. The sulfonamides were found stable throughout the study. The procedures of the accelerated and long-term stability tests were outlined.

NORMAN HO

CLEANING OF GREASE FROM INJURIES

Cleaning of Grease from Injuries, Queries and Minor Notes, J. Am. Med. Assoc. 164:826 (June 15) 1957.

The routine use of carbon tetrachloride in removing grease from minor cuts incurred by industrial workers has been questioned. Two consultants agree that, although carbon tetrachloride is not absorbed through the skin in toxic amounts, repeated inhalation of small amounts of the solvent is extremely hazardous, especially to those dressing such wounds. Suggested for use are acid-type detergent hand cleaners and acetone, if an organic solvent is necessary. The U. S. Public Health Service has reported on the use of waterless hand cleaners to the Wright Air Development Center (WADC T.R. 55-467).

JOHN D. LUCASSE

CONTACT DERMATITIS DUE TO HYDROCORTISONE OINTMENT

Contact Dermatitis Due to Hydrocortisone Ointment, Sams, W. M. and Smith, J. G., Jr., J. Am. Med. Assoc. 164:1212 (July 13) 1957.

A case of severe allergic contact dermatitis has been reported from the use of a hydrophilic ointment. (Cort-Dome creme 1%). The dermatitis developed even though the ointment contained 1% hydrocortisone. Patch testing proved the sensitization resulted from an allergy to free and sulfated higher alcohols (12-18 carbon-atom chains) contained in the ointment. One of these was sodium lauryl sulfate. Although reactions to these substances are relatively rare they are often severe. Therefore, it is recommended that specific information regarding the composition of ointment bases should be more readily available.

JOHN D. LUCASSE

DEODORANTS AND ANTIPERSPIRANTS

Deodorants and Antiperspirants, Klarmann, Emil G., Drug and Cos. Ind. (Part I) 81:36 (July) 1957 and (Part II) 81:176 (Aug.) 1957.

The first part of this article deals with the general mechanism of perspiration. Sweat is produced from eccrine glands (distributed all over the body) and apocrine glands (located particularly under the arms). The normal output of perspiration varies from one to three pounds per twenty-four hour period. Perspiration is composed of organic and inorganic residue.

The origin of perspiration odor resides primarily in the decomposition of organic material of protein and lipid character due to bacterial attack and decomposition.

In formulating antiperspirants, one usually proceeds upon the premise that some astringent chemical is needed in order to inhibit the flow of perspiration. So-called antiperspirant cosmetics act essentially as deodorants via two mechanisms—inhibition of bacterial activity and neutralization of odor by chemical combination with the odorous agent.

The protein coagulating potential of aluminum salts depends upon the anion. The inorganic salts are powerful coagulants, while the organic salts of aluminum are weaker in action. A protein precipitant is not necessarily an acceptable antiperspirant.

The second part of the article deals with the formulation of deodorants and antiperspirants and the role of various types of agents which may eliminate perspiration odor. Suggested formulations for liquid, cream, powder and cologne type antiperspirants are given. A high degree of acidity generated by hydrolysis of aluminum salts poses a problem in formulation. Such acidity may irritate the skin, have a destructive or staining effect on certain fabrics. To overcome this problem, formulations generally include inhibiting or buffering agents, or they may utilize metal compounds developing a lower degree of acidity without the aid of buffers. Examples of such formulations are described.

Micrococcus pyogenes var. *aureus* and *albus* and possibly an unidentified gram-positive bacillus appear to be primarily involved in producing the malodor of perspiration. Since this organism does not grow in acid media (lower limit is pH 5.6), an antiperspirant based upon a hydrolyzing metal salt which develops a markedly low pH should be effective in inhibiting growth of this bacteria by virtue of this acidity.

Deodorant preparations without antiperspirant action are effective due to the antibacterial agent present in the formulation. These agents, such as hexachlorophene, suppress odors by reducing or suppressing bacterial proliferation and biological activity. Antibiotics such as tyrothricin, neomycin and chlortetracycline proved effective agents in controlling perspiration odors but the disadvantage of using antibiotics for such purposes is obvious.

The significance of chlorophyll as a deodorant has dwindled. Taken internally chlorophyll's effectiveness as a deodorant is negligible. It is effective when in direct contact with odorous material. It is postulated that the effectiveness is due to either oxidation of odorous material or to its binding effect on odorants by physical absorption.

A new principle has been introduced into the field of deodorants. It involves certain ion exchange resins which take up lactic acid, ammonia and urea of sweat *in vitro*.

Pharmacodynamic agents of the cholinergic and anticholinergic types are being studied since eccrine sweating is a cholinergic process and apocrine sweating is of adrenergic origin. None of the available drugs in these classes lend themselves for routine cosmetic use because of undesirable collateral action.

EDWARD SUPERSTINE

REDUCING SUBSTANCES FROM RUBBER CLOSURES

Release of Reducing Substances from Different Kinds of Rubber Closures, Kondal, J., Farm. Tid. 66:210 (1956). Translation of an abstract from Pharm. Acta. Helv. by K. Munsel.

It was found that sterile water, which had been autoclaved in containers closed with 46 different kinds of rubber closures, appeared to contain too large an amount of reducing substances when assayed according to the Danish Pharmacopoea, 1948.

The author recommends the use of rubber wrapped in nylon foil for closing of vials and infusion bottles.

The use of undefatted cotton, wrapped in gauze, leads also to an undesirable release of reducing substances. It is recommended that the cotton be wrapped in nylon or teflon foil.

J. Wouter Huisman

RUBBER CLOSURES FOR COLLYRIA

Concerning the Unsuitability of Rubber Closures for Collyria, Heigard, J. J., Farm. Tid. 66:276 (1956). Translation of an abstract from Pharm. Acta Helv. by K. Munsel.

Collyria with zinc sulfate or with atropine sulfate were autoclaved in vials with different rubber closures. The amount of zinc sulfate decreased by five to eight %, the amount of atropine sulfate by seven to twenty-six percent.

This decrease is said caused partly by reducing substances released from the closures, partly by absorbing properties of the closures.

J. Wouter Huisman

SEQUESTRANTS, CHEMISTRY AND APPLICATIONS

Pharmaceutical Aspects of Sequestering Agents, Delgado, J. N. and Burlage, H. M., Am. Prof. Pharm. Part I 23:529 (June) and Part II 23:620 (July) 1957.

Chemical compounds possessing the pharmaceutical significance of deactivating metallic ions through the formation of soluble complexes or chelates have gained considerable application in the pharmaceutical industry. These compounds are referred to as sequestering agents or sequestrants. Other terms often used synonymously are chelating agents, complexing agents, complexons, and peptizing agents. Their background, chemistry and applications are reviewed in this paper.

Sequestration may be defined as the formation of soluble complexes or chelates of metallic ions by a reaction which involves a combination of an electron donor and an electron acceptor. The sequestering agent functions as the electron donor. If the metallic atom is not a part of a cyclic molecular structure, the compound formed is termed a complex. Conversely, if the metallic atom does form a part of a cyclic structure the compound is referred to as a chelate. The electron donor atoms in the sequestering agents are limited almost entirely to oxygen, nitrogen and sulfur. If, however, the metal is bound to carbon, the compound formed is not considered a chelate or a complex, but rather an organo-metallic compound. Originally, the term sequestration was chiefly applied to instances where precipitation of cations was minimized or eliminated entirely. Today the sequestering agents have been extended to alter the biological or chemical properties of a metallic ion in reactions other than precipitation processes.

Chemical properties of sequestrants, the chelating equilibrium constant "K" which expresses the extent to which chelate formation occurs, Zwitter ion formation, and stability with reference to temperature and dielectric constant are discussed in some detail in order to give the reader a more complete knowledge of the sequestration phenomenon.

Inorganic sequestering agents have been found to exist but the organic sequestrants possess far greater pharmaceutical significance. This latter group is generally subdivided into two categories; the aminopolycarboxylic acid derivatives and the hydroxy-carboxylic acids.

Ethylenediaminetetraacetic acid, or E.D.T.A. is the more extensively used compound of the first subdivision and has found wide application in pharmacy and other industrial processes. Its sodium salt, which is very soluble in water, is available under the following proprietary names: Tetrasodium Versenate, Sequestrene Na_4, Irgalon, Trilon, and Calsol. Application of the sequestering phenomenon through the use of E.D.T.A. can be illustrated as follows: (1) the stabilization of ascorbic acid solution through the chelation of trace amounts of iron, copper, and manganese ions which have a pronounced catalytic effect on the oxidation of ascorbic acid; (2) as a water softening agent in the field of detergents (sequestering agents are generally expected to overcome completely the limitations of soap in hard water), and as an excellent preservative or rancidity retardant for soaps by inhibiting the catalytic effects of trace metals; (3) in analytical titrations suitable indicators will change color when all the cation has been sequestered and a slight excess of reagent is present—E.D.T.A. also finds application in gravimetric, potentiometric, and polarographic methods; (4) 1.5% in five % glucose solution added to 400-500 ml. of blood proved a very suitable preservative by sequestering calcium ions; (5) the treatment of lead poisoning through the use of the sodium calcium salt of E.D.T.A.; (6) stability of emulsions and clarity of shampoos is maintained by adding 0.1 to 1% E.D.T.A.; and (7) in the field of urology experiments have been conducted to determine the feasibility of using E.D.T.A. in the treatment of urinary calculi.

Other amino-carboxylic acid derivatives include nitrilotriacetic acid, di(hydroxyethyl) glycine, (hydroxyethyl)-ethylenediaminetriacetic acid, and diethylenetriaminepentaacetic acid.

Of the hydroxy-carboxylic acids which find extensive application in the field of pharmacy, citric and tartaric acids are the most commonly employed. Gluconic acid has also been employed as a sequestering agent, but the related compound, saccharic acid has been used only to limited extent.

Theodore J. Benya

POISONING FROM PETROLEUM DISTILLATES

Poisoning from Petroleum Distillates: The Hazards of Kerosene and Furniture Polish, Soule, A. B., Jr. and Foley, J. C., J. Maine Med. Assoc. 48:103 (April) 1957.

Petroleum distillates, particularly kerosene and furniture polish, are a frequent cause of accidental poisoning in children. Symptoms of poisoning are choking, gagging, and vomiting progressing to stupor and unconsciousness. Dyspnea and cyanosis often occur. The characteristic lesion is an acute fulminating and hemorrhagic bronchopneumonia which appears within minutes or several hours of exposure, reaches its peak in 3 to 12 hours, and in nonfatal cases, subsides over a period of from hours to several days. Treatment consists mainly of the administration of oxygen to alleviate respiratory distress and combat cyanosis. The authors advocate educational campaigns to acquaint the public with the hazards of petroleum distillates.

John D. Lucasse

PROTECTIVE COATING FOR PLASTER CASTS

Protective Coating for Plaster Casts, Sakson, J. A., Am. Med. Assoc. 164:487 (May 25) 1957.

In fracture cases plaster casts are often seriously weakened by the writings, carvings, and repeated washings to which they are subjected. Spraying such casts with Krylon (Dupont) plastic from a pressurized can imports a glass-like finish to their surfaces, resulting in increased strength and resistance to water.

John D. Lucasse

Because of the interest in this Section of THE BULLETIN, plans are being made to develop it further in the interest of practicing hospital pharmacists. Anyone wishing to contribute abstracts, please write to the Editor indicating your particular interest.

In addition to abstracting English language articles, we need pharmacists to abstract and translate into English pharmaceutical articles written in the following languages: Danish, Norwegian, Portuguese, Spanish, Swedish and Russian. If you have a reading knowledge of one of these languages and are interested in contributing to Selected Pharmaceutical Abstracts, please contact the Editor of THE BULLETIN.

ACTION OF EMOLLIENT CREAMS ON SKIN

Action of Emollient Creams and Their Additives, Blank, J. H., J. Am. Med. Assoc. 164:412 (May 25) 1957.

The action of emollients by which they combat dryness of the skin has often been described as a lubricating process, *i.e.*, a reduction of friction between the lamellae of the stratum corneum. However, studies have shown that water is the only plasticizer of keratinized tissue and that emollients act principally as surface agents, keeping the skin flexible by forming an occlusive layer which retards the loss of water from the stratum corneum. Because the major barrier to water loss from the body is below the stratum corneum and the natural lipid film on the skin is an inadequate barrier to water loss, the stratum corneum is easily dehydrated. Thus when the relative humidity of the atmosphere is low, the skin frequently becomes dry and inflexible. Flexibility is further reduced if, through physical, chemical, or pathological stimuli, the stratum corneum is thickened. In these instances emollients are invaluable.

In an effort to increase the emollient action of creams, certain agents have been added to them. Vitamin A, when taken orally, will correct the abnormal keratization which characterizes many skin diseases. When applied topically vitamin A is known to penetrate the skin; however, there is still little evidence to show that emollients containing it are of greater value than the emollients alone.

Estrogens have been added to emollients in a effort to delay or reverse the symptoms of dryness and loss of elasticity which occurs in skin during normal aging. Although it has been established that estrogens are absorbed by the skin, there is no conclusive evidence proving their value in altering the aging process.

JOHN D. LUCASSE

BETA-PROPIOLACTONE, A STERILIZING AGENT

Beta-Propiolactone in Sterilization of Vaccines, Tissue Grafts and Plasma, Hartman, F. W. and Lo Grippo, G. A., J. Am. Med. Assoc. 164:258 (May 18) 1957.

The sterilization of vaccines, tissue grafts, and plasma involves, beyond the destruction of microorganisms, the preservation of proteins in or near their original state. Studies show that beta-propiolactone is a superior sterilizing agent for these biologicals because of its rapid and irreversible action, minimal alteration of proteins, and complete hydrolysis, obviating neutralization and toxicity. Protein preservation and relatively nontoxic end products make it the most promising agent for the sterilization of blood plasma. Rapid bactericidal and virus inactivating properties with maintenance of comparatively high antigenicity offers a method for production of improved vaccines. Activity on a wide range of bacteria, fungi, and viruses, plus a rapid penetration of tissues, opens the way for safer and more plentiful tissue grafts.

Beta-propiolactone is available from the B. F. Goodrich Company.

JOHN D. LUCASSE

CROSS INFECTION FROM THERMOMETERS

Cross Infections from Thermometers, Editorial, J. Am. Med. Assoc. 164:669 (June 8) 1957.

In the elimination of the clinical thermometer as a source of cross-infection in hospitals the use of an individual thermometer for each bed is ideal. However, many hospitals still employ the communal thermometer. In these instances the use of a rapid-acting sterilizing solution becomes imperative. Mercuric chloride (1:10,000) and mercuric iodide (1:1000) have been shown to be ineffective. Benzalkonium chloride, 1:1000 in 70% isopropyl alcohol and iodine, 0.5%, also in alcohol, were found to sterilize thermometers completely in 10 minutes. Alcohol alone was not effective. Wiping thermometers with a soapy pledget before immersion increased the efficiency of any solution.

JOHN D. LUCASSE

TABLET DISINTEGRATION

Tablet Disintegration with Cellulose, Bequette, R. J. and Huyck, C. Lee, Drug and Cos. Ind. 81:166 (Aug.) 1957.

A study was made to determine the comparative effectiveness of starch and cellulose as tablet granule disintegrants. Purified cellulose has lubricating and binding properties and it is accepted by the F.D.A. for tablet formulation.

Five and ten % concentrations of dry starch and cellulose were added to lactose and calcium carbonate for tablet compression. Five % acacia solution was used as the granulating agent. Compression hardness of the tablets was kept constant. The U.S.P. method for testing disintegration time was followed.

The authors concluded that purified cellulose at 5% concentration gave faster disintegration than starch in ten out of twelve formulations tested. Further, cellulose would be a ready substitute for starch when tablet compression difficulties are encountered concerning lubricants, binding agents and disintegrants. Since purified cellulose is white, no color is imparted to tablet formulations. Cellulose could be used in cases where faster disintegration is desired.

CLIFTON J. LATIOLAIS

DRUG RELEASE FROM TOPICAL APPLICATIONS

Drug Release from Topical Applications, Gemmell, D.H.O. and Morrison, J.C., Phar. J. 179:47 (July 20) 1957.

The problems of measurement of drug release from topical preparations are succinctly discussed. Factors influencing drug penetration and absorption through intact skin are mode of application, the vehicle, the lipoid solubility of the drug, and the partition coefficient of the drug between its vehicle or base and the dermal secretions such as sweat, sebum, tissue lipoids and extracellular fluids.

A classification of methods used for evaluating drug release from topical application includes: (1) *In vitro* methods which utilize diffusion and membrane technics through chemical or microbiological assay; (2) *In vivo* methods involving the

analysis of blood, urine, feces, and organs or biopsy and histological examinations; (3) clinical methods; and (4) radio-active tracer methods.

In vitro methods are of limited value since they give an indication of the ability of the base to liberate the medicament under the conditions of a particular test. *In vivo* methods use living test animals to determine both penetration and absorption of the medicament and the results of animal experiments are extended to problems concerning human beings. Clinical methods do not readily assist in the evaluation of drug release. Radioactive tracer techniques have been used thus far in limited applications.

In spite of these varied methods, there is no one test which solves simultaneously the three problems of measurement of drug release, namely, (1) the rate of liberation, (2) the degree of penetration, and (3) the rate and degree of absorption. This leaves much to be desired in the rational selection of vehicles for the formulation of topical preparations. Choosing the proper vehicle according to the drug used, the therapeutic aim, and the condition being treated or to control the level of activity of the incorporated drug remains to be solved by standard tests.

CLIFTON J. LATIOLAIS

TEST FOR RUBBER CLOSURES

Extraction Tests for Rubber Closures, Morrisey, E. J., Jr. and Hartop, W. L., Jr. Drug Standards 25:1 (Jan.-Feb.) 1957.

A procedure is presented to control the specifications of rubber closures for parenteral solutions. The closures are autoclave extracted with distilled water. The resulting extract is evaluated (1) for turbidity, expressed in nephelos units, with the nephelometer, (2) for reducing agents by iodine titration, and (3) for a shift in pH potentiometrically.

The following standards were proposed as acceptable limits: not more than 40 nephelos units for turbidity; not more than 0.5 ml for 0.01N iodine titration; and pH 5-7.

NORMAN HO

STABILITY OF ASCORBIC ACID AND CYANOCOBALAMIN SOLUTIONS

The effect of Antioxidants on the Stability of Ascorbic Acid and Cyanocobalamin Solutions, Kallelis, T. S., Dissertation Abstracts 17:1536 (July) 1957.

The effect of certain antioxidants upon the stability of ascorbic acid, cyanocobalamin and ascorbic acid-cyanocobalamin solutions was investigated in various formulations. The antioxidants employed were sodium bisulfite, potassium cyanide, thiourea, glycine, thioglycerol, glutathione, thiopropionic acid, sustane (butyl hydroxyanisole), melilotin (dihydrobenzopyrone), NDGA (nordihydroguaiaretic acid), ethyl hydrocaffeate, sequestrene Na_2 (disodium ethylenediamine tetraacetate), and sequestrene Na_3 (trisodium ethylenediamine tetraacetate). The liquid formulations included distilled water redistilled in an all glass apparatus, aqueous solutions buffered to pH 6.0, syrup, and citric acid syrup.

The concentrations of the solutions were 25 mg/ml for ascorbic acid and 20 mcg/ml for cyanocobalamine. All solutions were stored at room temperature or at 42°C.

While the investigation found that the antioxidants and sugar itself enhanced the stability of ascorbic acid solutions, the stability of ascorbic acid was further increased in those formulations containing both antioxidants and sugar. However, antioxidants had deterimental effects on cyanocobalamin in distilled water. The pH, antioxidants and type of vehicle were factors influential on the stability of cyanocobalamin.

The stability of ascorbic acid-cyanocobalamin combination was increased with formulations (1) maintaining a pH 5-7, (2) using syrup, and (3) including antioxidants such as sodium bisulfite, potassium cyanide, and sequestrenes in concentrations of 0.025 to 0.1 percent.

NORMAN HO

current literature

. . . also calling your attention to the following articles appearing in recent hospital and pharmaceutical journals

ADMINISTRATION

—GENERAL

McLemore, Gilbert: The Administrative Pharmacist, *Hosp. Management* 84:120 (Oct.) 1957.

—PERSONNEL

Benya, Theodore: Selection Guides for Pharmacy Departments, *Am. Profess. Pharm.* 23:788 (Sept.) 1957.

—POLICIES

Hassan, William E.: Ensuring Safety in Drug Administration—Do you Have Adequate Policies, *Hosp. Management* 84:108 (Sept.) 1957.

Sister Mariel: Handling Drug Samples, 38:74 (Aug.) 1957.

—PURCHASING

Bowles, G. C., Jr.: How the Purchasing Agent and Pharmacist Can Work Together, *Hospitals* 31:64 (Oct.) 1957.

Earngey, Willard P., Jr.: What I Require—and What I Expect—from My Purchasing Department, *Hospitals* 31:64 (Sept. 16) 1957.

Terenzio, J. V.: Some Legal Aspects of Hospital Purchasing, *Hosp. Management* 84:126 (Oct.) 1957.

Jeffries, S. B.: Needed: Scientific Management of Drug Resources, *Hospitals* 31:60 (Sept. 16) 1957.

—STORAGE

Teplitsky, Benjamin: Devises Procedure for Inspecting Drugs, *Am. Druggist* 136:53 (Sept. 23) 1957

PROFESSIONAL

—ETHICS

Sister Mary Maurice: Substitution Is Not Deception, *Hosp. Progress* 39:124 (Sept.) 1957.

CIVIL DEFENSE

Anon.; Pharmacists' Indoctrination Course in Civil Defense, *Hosp. Pharm.* (Canada) (July-Aug.) 1957.

Fryer, G. E.: General Information on Civil Defense Health Service Planning, *Hosp. Pharm.* (Canada) 10:195 (July-Aug.) 1957.

Pace, F. C.: Atomic Weapons with Casualty Effects, *Hosp. Pharm.* (Canada) 10:206 (July-Aug.) 1957.

Summers, J. L.: Refresher Course in Hospital Pharmacy, *Hosp. Pharm.* (Canada) (July-Aug.) 1957.

PHARMACOLOGY

Anon.: Pharmacologic Actions of Cardiac Glycosides, *Modern Hosp.* 89:102 (Aug.) 1957.

PHARMACY AND THERAPEUTICS COMMITTEE

—INVESTIGATIONAL DRUGS

Hassan, William E.: Research Drugs and Their Use in Hospitals, *Am. Profess. Pharm.* 23:700 (Aug.) 1957.

PUBLIC HEALTH

—POISON CONTROL

Parker, Paul F.: Poison Control . . ., *J. Am. Pharm. Assoc., Pract. Pharm. Ed.* 18:489 (Aug.) 1957.

ASHP affiliates

Indiana Chapter

The regular quarterly meeting of the Indiana Chapter of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS was held at the Sheraton French Lick Hotel, at French Lick, Indiana, on June 18, 1957, at 7:00 P.M., in conjunction with the annual convention of the Indiana Pharmaceutical Association. A dinner was enjoyed by members and their guests prior to the business session.

A short talk on the "Servicing of a Small Hospital by a Retail Pharmacist," along with comments on the advantages of belonging to the hospital society, was given by Mr. Charles Schreiber.

General plans for the coming year were discussed. It was announced that the chapter would participate in the meeting of the American Association for the Advancement of Science, which is to be held in Indianapolis in December.

Special guests at the meeting included: Mr. and Mrs. Ivan Holder, President of the Indiana Pharmaceutical Association; Mr. and Mrs. Henry Heine, Secretary of the Indiana Pharmaceutical Association; and Miss E. Charles of Puerto Rico.

New officers of the Indiana Society who were installed at the June meeting include *President,* William Wissman, Ft. Wayne; *Vice-President,* Richard Glenn, Evansville; and *Secretary-Treasurer,* Mildred Wiese, Indianapolis.

Louisiana Society of Hospital Pharmacists

Members of the Louisiana Society of Hospital Pharmacists met at Arnaud's Restaurant in New Orleans on August 1 for the installation banquet. Mr. Albert Lauve, retiring President, served as Master of Ceremonies.

New officers elected to serve during the coming year include *President,* Joseph Crisalli, U. S. Public Health Service Hospital, New Orleans; *Vice-President,* Troy Carter, U. S. Veterans Hospital, New Orleans; *Secretary,* Herbert J. Mang, Ochsner Foundation Hospital, New Orleans; and *Treasurer,* Dorothy Haindel, Ochsner Foundation Hospital, New Orleans.

Southeastern Society of Hospital Pharmacists

Mr. William W. Taylor, President of the Southeastern Society of Hospital Pharmacists has announced committee appointments for the coming year. Chairmen of the various committees are as follows: *Convention Committee*: Carl M. Dell, Jackson Memorial Hospital, Miami, Fla.; *Projects Committee*: Jack Kirkland, Miner's Memorial Hospital, Williamson, W. Va.; *Publications Committee*: C. Joseph Vance, South Highlands Infirmary, Birmingham, Ala.; *Membership Committee;* Virginia Caudle, City Hospital, Winston-Salem, N. C.; *History Committee*: Lillian Price, Emory University Hospital, Atlanta, Ga.; and *Board of Canvassers*: Ernest W. Rollins, Baptist Memorial Hospital, Winston-Salem, N. C. Delegates to the Annual Meeting of the ASHP include Lillian Price and Grover C. Bowles with Rudolph W. Hardy and Jack C. Kirkland serving as alternates.

Southern California Society of Hospital Pharmacists

The July meeting of the Southern Society of Hospital Pharmacists was held at the Hollywood Presbyterian Hospital in Los Angeles. The meeting was opened by Jack S. Heard, President. Miss Marie Tilley, chief pharmacist, of the hospital was first introduced and in turn presented members of her staff.

Mr. Heard gave a report on the June Institute on Hospital Pharmacy held in Seattle and attended by twelve of the local members.

Following this, he presented a summary of plans for the Seminar to be sponsored by the Southern California Society at the University of California's Lake Arrowhead Lodge over the Labor Day weekend.

A letter from Sister Junilla, Queen of Angels Hospital, was next read. Sister Junilla thanked the group for the many cards and letters sent to her during her recent illness.

Mr. Ernest Kelso, Chairman of the Inter-Professional Committee reported on events at the recent California Pharmaceutical Association Convention in Coronado. He announced that all California pharmacists are now eligible to join that group. In the past membership was limited to store owners.

Dr. George Archambault, Pharmacist Director, U. S. Public Health Service, famed as a pharmacy teacher, lawyer and author, was next introduced as the featured speaker. He presented a most informative talk on the legal responsibilities of hospital pharmacists. Dr. Archambault presented a clear, comprehensive analysis of the subject, explaining how current laws and their applications were developed over the years.

Miss Tilley and her staff next entertained the group at the social hour following the meeting.

Kansas City Hospital Pharmacists

Members of the Society of Hospital Pharmacists of Greater Kansas City met at the Blue Cross, Blue Shield Building in Kansas City on May 15 at 2 P.M. The meeting was presided over by Mr. Charles Loomis who introduced the guest speaker, Miss Sue Jenkins, Executive Director of the Kansas City Area Hospital Association. Miss Jenkins informed the group that the Society of Hospital Pharmacists of Greater Kansas City had been accepted as an affiliate member of the Kansas City Area Hos-

pital Association. She attended the meeting to discuss ways in which the Hospital Association could be helpful to the hospital pharmacists. Possible areas in which the two organizations might work together were suggested including membership, formulary for all hospitals of the city and the advisability of group purchasing.

During the business session, Sister Joseph Marie presented a report on the Annual Meetings of the American Pharmaceutical Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS which were held in New York City in April.

Akron Area Society of Hospital Pharmacists

The first fall meeting of the Akron Area Society of Hospital Pharmacists was called to order by President Theodore Mink at 7:45 P.M. on September 10 at Akron General Hospital. Sixteen members and three guests were present. Announcement of the new officers to serve during the coming year include *President* Theodore Mink, Akron General Hospital, Akron; *Vice-President* John V. McGowan, Green Cross General Hospital, Cuyahoga Falls; *Secretary* Samuel E. Arlow, Akron City Hospital, Akron; and *Treasurer* Paul Dickerson, Aultman Hosiptal, Canton.

Business transacted during the meeting included a report on the Student Visit Project, reference to membership in the national organization and members' attention was called to the fact that affiliation with the national organization is essential to holding membership in the Akron Area Society.

Plans for the new year were outlined and the President made committee appointments. Meetings are scheduled as follows:

October 16—Decennial Meeting (all day), Akron
November 12—Alliance
December 10—Warren
January 14—Cuyahoga Falls
February 11—Barberton
March 11—Youngstown
April—Open
May—Open
June 8—Social meeting

Plans have been made to hold an all day meeting celebrating the Decennial of the Akron Area Society of Hospital Pharmacists. This will be held at the Eva P. Craig Auditorium in Akron and the Ohio Society has been invited to meet with the Akron group. The program includes a discussion of radioactive pharmaceuticals and the hospital pharmacist, a talk on poison control centers, and a discussion of the American Formulary System.

Michigan Society of Hospital Pharmacists

The Michigan Society of Hospital Pharmacists met at Metropolitan Hospital in Detroit on September 19. Mr. Ed Superstine, Chief Pharmacist, acted as Host.

The meeting was opened by President Maxwell Miller who introduced Dr. Kenneth E. McIntyre, Director of Metropolitan Hospital and Clinics. Dr. McIntyre welcomed the group and gave them some background regarding the history and operation of the hospital. The Program Chairman, Mr. Clifton J. Latiolais, introduced the principal speaker, Dr. Robert B. Cubberley, Department of Internal Medicine, Metropolitan Hospital. Dr. Cubberley very ably discussed "A Physician's View of a Hospital Pharmacy," giving those present some pointers on how hospital pharmacists might be more helpful to the medical staff and in turn to the patient in the hospital.

During the business session, there was a general discussion regarding plans for meetings during the year and suggestions for the program. Also a letter from the Secretary of the National Organization, Gloria Francke, was presented, asking the Michigan Society to indicate whether or not they wish to have the 1958 H.A.K. Whitney Award presented at the ASHP Annual Meeting. After general discussion, it was moved and carried that the Michigan Society again have the award presented at the Annual Meeting. However, this action was taken for 1958 only and the Michigan Society will continue to select the recipient and provide for his attending the Annual Meeting.

Colorado Society of Hospital Pharmacists

At the July 16 meeting of the Colorado Society of Hospital Pharmacists, Mr. Sam Kohan presented a review of the Seattle Institute on Hospital Pharmacy. Among the topics covered were the role of the hospital pharmacist, human relations and communications, Pharmacy and Therapeutics Committee, responsibility of a hospital pharmacist for drug information, oral diabetic agents, training programs for hospital pharmacy interns, control of hospital infections, poison controls, and handling radioisotopes. Mr. Irvin Friesen and Mr. Ellsworth West, who also attended the Institute, added further details and interesting sidelights.

The meeting was held at the Cosmopolitan Hotel in Denver and the group was entertained at a dinner sponsored by McKesson and Robbins.

The Colorado Society held its August 20 meeting at the Denver General Hospital. The program included a group discussion on "Problem Solving," under which various subjects were discussed including orders which are not clear, vacation replacements, and contacting physicians regarding overdosages.

During the business meeting, plans were discussed for the program during the coming year with emphasis to be placed on membership and working toward affiliation with the national organization.

Illinois Society of Hospital Pharmacists

The annual joint meeting of the Chicago Branch of the A.Ph.A. and the Illinois Society of Hospital Pharmacists was held on Wednesday evening, May 11 at the Illini Union Building. Following the dinner, new officers for the various organizations were installed with Mr. Louis Gdalman doing the honors for the Illinois Society of Hospital Pharmacists and Dr. George Webster for the Chicago Branch of the A.Ph.A. as well as the Student Branch at the University of Illinois College of Pharmacy.

Following the installation ceremonies, a lecture on "Marketing Research," was presented by Mr. Ray Martinque.

Philadelphia Association

The Philadelphia Hospital Pharmacists' Association opened its twentieth year since organization at the September 17 meeting held at the Jefferson Medical College Hospital. Business transacted during the meeting included a report on the Speakers' Bureau, a report from the Committee on Constitution and By-Laws and arrangements being taken care of by the Transportation Committee.

as the president sees it

LEO F. GODLEY

Bronson Methodist Hospital
Kalamazoo, Michigan

The past two months have been busy, what with the traveling, and telephoning, and telegraphing, and corresponding.

It was a great experience, meeting with the Canadian Society of Hospital Pharmacists in Montreal on their tenth anniversary. It's surprising how much at home we feel when we go to Canada. I'm sure that it's because the Canadians have meant so much to us in the growth and development of our own organization. Seeing the many familiar faces and complete similarity of purpose, it was difficult to realize that I had just crossed an international boundary. I would like to say a great deal about the meeting and the people. Right now, I remember the young and energetic President Summers from Saskatoon and the creditable job he did in a difficult executive session; the tact and wisdom of our good friend Isabel Kippen Stauffer discussing from the floor; the unassuming, dedicated Sister Ancilla accepting great praise with humility. God bless the Canadians!

Through the medium of a Pfizer Seminar, I got over to Los Angeles to meet with the Southern California group. The meeting was held at Lake Arrowhead high up in the mountains; and a good meeting it was with Charlie Towne and Jack Heard managing with efficiency and enthusiasm. I had a chance to discuss Executive Committee plans a bit with Charlie Towne (Chairman of the Committee on Pharmacists in Government Service); and it was good to hear that Jack Heard is getting quite involved in local planning committee activities for the Annual Meeting in Los Angeles next April.

The American Hospital Association Institute at Chicago in August was, as usual, a successful venture. It was over subscribed again; and interestingly enough, again, most of the students were attending their first Institute.

One particularly pleasant thing for me at this Institute was that my wife, Ann, was able to come in on Thursday. I enjoyed introducing her to people whom she knew so well but had never met in person. It was also good to see her renew some old acquaintances. As many of you know, Ann is a hospital pharmacist; but this is the first professional meeting she has been able to attend for about ten years.

In Chicago, Gloria Francke, Paul Parker, and I met with AHA's Bates, Oddis, and Swift and evolved a suggested administrative procedure for Hospital Pharmacy Institutes . . . Joe Oddis told me today by 'phone that Philadelphia was being considered for one of next year's Institutes.

I am sure now is the best time to urge that everyone read the "green sheets" that were published in the last issue of THE BULLETIN. You'll be amazed and delighted at the newsworthy and noteworthy programs that are developing in your SOCIETY. After studying these proceedings you will be rewarded by a greater understanding and appreciation of SOCIETY government and activity. And this understanding and appreciation are necessary for progress.

We are planning two Executive Committee meetings this year, one in Washington during the meeting of the Pan-American Congress on Pharmacy and Biochemistry and another in January. I would like to ask that those of you who might have suggestions for any of the committees to write the chairman today. I know Ethel Pierce would like to hear from you on Professional Liability Insurance and Robert Lantos is collecting information on a problem of international interest, safety practice and procedures. Don Francke is having a special meeting soon with his Constitution and By Laws Committee; and Ben Teplitsky is anxious to get reports on special projects.

I am looking forward to meeting with the Board of Selection of the Committee on Research and Development in New York early in October. I hope that everyone has submitted their requests for research grants. Certainly, through this committee, many of the hopes for hospital pharmacy can become lasting realities. On this same trip, I shall attend the Convention of the American Hospital Association and participate on the program in a panel discussion of the Formulary System. Also, while in the East, we will meet to continue our discussion with the National Pharmaceutical Council.

Recent word from Chairman Heller of the Committee on Pharmacy and Pharmaceuticals indicates that the American Hospital Formulary will be available next spring. I have had many anxious comments about this service all over the country and this is certainly good news.

Mr. Bogash and Mr. Latiolais, I and the entire membership of the SOCIETY extend to you our hearty congratulation and best wishes as our new officers-elect. How fast time passes!

NEWS

Bogash and Latiolais to Head ASHP

Robert C. Bogash

Clifton J. Latiolais

Robert C. Bogash, Director of the Pharmacy Department at Lenox Hill Hospital in New York City, has been elected president of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS for the 1958-1959 term. The Vice-President-Elect is Clifton J. Latiolais, Assistant Director of the Audit of Pharmaceutical Service in Hospitals, which is being carried out through the Division of Hospital Pharmacy of the American Pharmaceutical Association and the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS.

Mr. Bogash has served the SOCIETY in numerous capacities, having been a member of the Executive Committee, Chairman of the Committee on Program and Public Relations, Chairman of the Special Projects Committee, and active in the Southeastern New York State Chapter of the ASHP. He is a graduate of the Philadelphia College of Pharmacy and Science and was previously Chief Pharmacist at the Memorial Hospital in Wilmington, Delaware.

The Vice-President-Elect, Mr. Latiolais, has served on the Executive Committee and as Chairman of the Committee on Minimum Standards for the past two years. He is a graduate of Loyola University College of Pharmacy and holds a Masters degree from the University of Michigan. Prior to accepting his present position, he was Chief Pharmacist at Strong Memorial Hospital in Rochester, N. Y.

The Secretary and Treasurer of the SOCIETY are elected for three-year terms. The term of the present Treasurer, Sister Mary Berenice of St. Louis, Missouri, expires with the 1959 Annual Meeting. The term of the Secretary, Mrs. Gloria Francke, expires at the 1958 Annual Meeting.

New officers will be installed at the SOCIETY's Annual Meeting which will be held in Los Angeles in April, 1958.

The ballots of the recent election were counted by a Board of Canvassers, consisting of four ASHP members appointed by President Leo F. Godley, and the results submitted to the Secretary, Gloria N. Francke. Included on the Board of Canvassers were R. David Anderson, King's Daughters' Hospital, Staunton, Va.; Franklin Cooper, George Washington University Hospital, Washington, D. C.; Herbert L. Flack, Jefferson Medical College Hospital, Philadelphia, Pa.; and Vernon Trygstad, Veterans Administration Central Office, Washington, D. C.

1958 Annual Meeting

Plans are being made for the 1958 Annual Meeting of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS which will be held in April in Los Angeles in conjunction with the Convention of the American Pharmaceutical Association. The program will be in charge of the Committee on Program and Public Relations which is headed by Mr. Walter Frazier, Chief Pharmacist at Springfield City Hospital, Springfield, Ohio. Those who wish to submit papers for presentation at the Los Angeles meeting must contact Mr. Frazier not *later than November 1.*

Local arrangements for the hospital pharmacy meetings will be in charge of Mr. Jack Heard, Chief Pharmacist at the University of California Hospital in Los Angeles. The 1958 H.A.K. Whitney Lecture Award will be presented at a dinner during the meeting and other special events will be arranged for hospital pharmacists.

A.Ph.A. Officers for 1958-1959

Officers of the American Pharmaceutical Association elected to serve during the 1958-1959 term include President, Louis J. Fischl, Oakland, Calif.; First Vice-President, Stephen Wilson, Detroit, Mich.; Second Vice-President Howell R. Jordan, Austin, Tex.; and Council Members-Elect, Troy C. Daniels, San Francisco, Calif.; J. H. F. Dunning, Baltimore, Md. and John A. MacCartney, Detroit, Mich. These officers will be installed at the annual Convention in Los Angeles, during the week of April 20, 1958.

1958 C.H.A. Convention

Rev. John J. Flanagan, S.J., Executive Director of the Catholic Hospital Association of the United States and Canada, has announced a change in the traditional May convention date of the Association. The 43rd Annual Convention has been scheduled for June 21-26 at Atlantic City, N.J.

"Because of many conflicts with Decoration Day travel and activities, the Executive Committee has voted to change the 1958 convention date to June 21-26," he said in a prepared statement sent to members.

Pre-convention meetings, including the annual meeting of the Conference of Catholic Schools of Nursing, will be held June 21-22. This would also include the C.H.A. Institute on Hospital Pharmacy which is held annually in conjunction with the convention.

The Convention will open June 23 and close June 26.

Honorary Degree to Sister Mary Berenice

Sister Mary Berenice Ripperger, S.S.M., the present treasurer of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, received an Honorary Degree of Doctor of Pharmacy at the Spring Commencement of the St. Louis College of Pharmacy and Science. In making the presentation, Sister Berenice was cited for her outstanding contributions to hospital pharmacy. Sister Berenice is well known to members of the ASHP through her work on the Executive Committee as well as other activities through a period of many years. She is also recognized for her work with the Catholic Hospital Association's Committee on Pharmacy Practice.

She is a graduate nurse as well as a pharmacist and has been active in the development of hospital pharmacy for many years. Her college education was obtained at St. Louis University and by attending private lectures given by Professor Francis Hemm, Dr. H. M. Whelpley and Dr. Otto A. Wall of the St. Louis College of Pharmacy.

Sister Berenice is Chief Pharmacist at St. Mary's Hospital, St. Louis, and Director of Pharmacy Service and a member of the Hospital Board of St. Mary's Group of Hospitals of St. Louis University. She also serves as a consultant for hospital pharmacy service in thirteen hospitals operated by the Sisters of St. Mary.

She is a life member of the American Pharmaceutical Association, a member of the American Association for the Advancement of Science and a charter member of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS. She was one of the organizers of the Catholic Hospital Pharmacy Guild of St. Louis which merged with the Hospital Pharmacists' Association of Greater St. Louis when it was formed some years later.

Gdalman to Head Pharmacies

Louis Gdalman

Dr. Karl S. Klicka, Director of Presbyterian-St. Luke's Hospital, has recently announced the appointment of Mr. Louis Gdalman as Director of Pharmacies for Presbyterian-St. Luke's Hospital. Mr. Gdalman has been associated with St. Luke's Department of Pharmacy since 1930.

A graduate of the University of Illinois College of Pharmacy as well as the University of Chicago's Physical Science Division, Chemistry, Mr. Gdalman is a lecturer on the Faculty of Northwestern University's School of Hospital Administration and on the Faculty for the American Hospital Association's Institute on Hospital Pharmacy. He has also served on the Guest Faculty for the Catholic Hospital Association's Hospital Pharmacy Institutes.

A member of the American Pharmaceutical Association and the Chicago group, Mr. Gdalman has been both President and Secretary of the Chicago Branch. He is a charter member of the Illinois and National chapters of the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS and has served as Secretary-Treasurer and President of the Illinois chapter.

Other memberships include: The Committee on Paramedical Services of the Illinois Hospital Association; American Chemical Society—National Society and Chicago branch; Rho Chi, the National Honorary Pharmaceutical Society; sustaining member of the Chicago Technical Council; Fellow, American Association for the Advancement of Science; and the American Hospital Association.

During World War II, Mr. Gdalman was a Chicago Civilian Defense War Gas Instructor, and in 1950, he served on several committees of the Chicago Medical Civilian Defense Council.

A native Chicagoan, Mr. Gdalman is married and has two children. His wife is a graduate of St. Luke's Hospital's School of Nursing.

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Presbyterian-St. Luke's Hospital, a consolidation of two of Chicago's oldest hospitals, St. Luke's and Presbyterian, is currently engaged in a $18,500,000 development program in Chicago's West Side Medical Center. It will be one of the nation's outstanding institutions of medical service, teaching and research.

A.C.A. Issues New Publication

The VOICE of the PHARMACIST is the name of a new weekly publication being launched by the American College of Apothecaries.

The "VOICE" as it will be known, will consist primarily of hard hitting editorial copy designed to bring to all pharmacists the true facts concerning developments in Pharmacy, Medicine, Industry, Government, Legislation and any other area which directly effects the future growth and survival of the profession. In addition it will present the latest information on drug products as well as point out the availability of useful and valuable information of both a professional and economic nature.

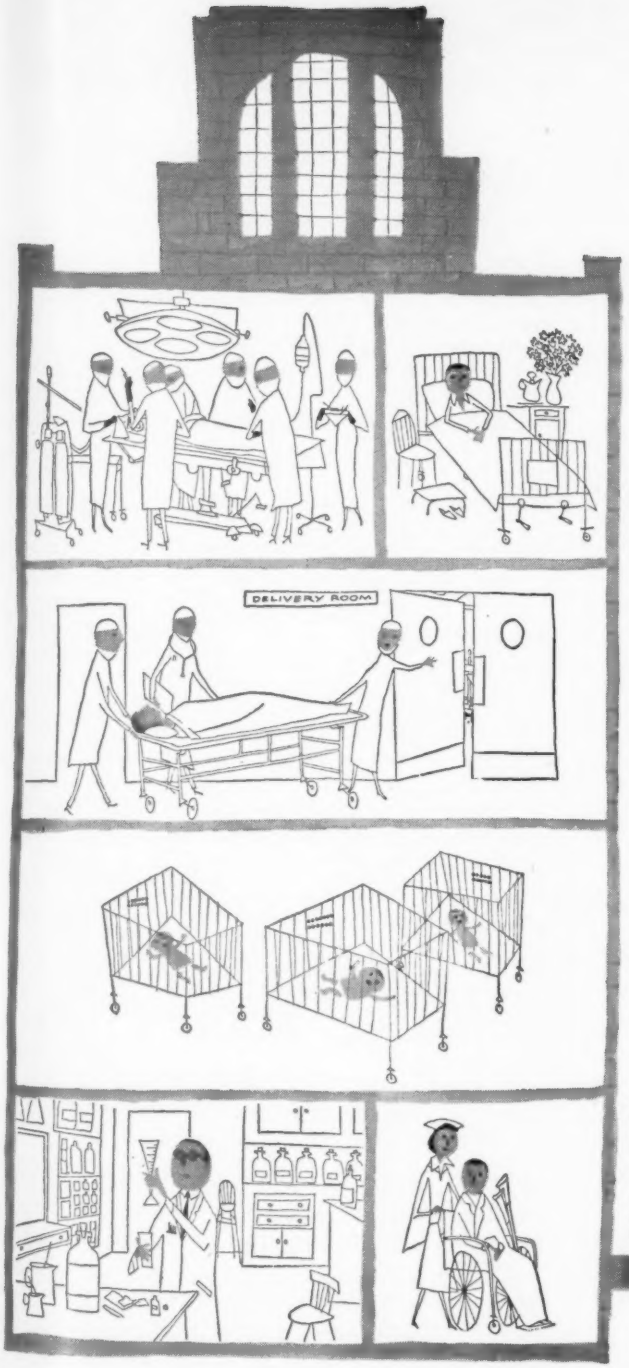
Being published on a weekly basis, the information will be timely and as up to date as possible.

Designed for the pharmacist who is sincerely interested in his profession, the "VOICE" will accept no advertising and will be published as a non-profit publication wholly supported by its subscription fees which will be $15.00 per year.

Impetus for this publication came from the extreme interest displayed in the A.C.A.'s Secretary's Newsletter. This interest by pharmacists led to the A.C.A.'s Board of Directors decision to expand this publication and make it available to every pharmacist.

Managing editor for the *VOICE of the PHARMACIST* will be Robert E. Abrams, Executive Secretary of the American College of Apothecaries who has served as editor of the Secretary's Newsletters for the past five years. A separate editorial staff will be responsible for the publication and every effort will be made to ensure that the "VOICE" brings to the pharmacists the information they need and can utilize.

The first issue of the "VOICE" is being planned for September 10th and will be sent to over 18,000 pharmacists throughout the country. Subscription information is available from: The VOICE of the PHARMACIST, American College of Apothecaries, Hamilton Court, 39th & Chestnut Street, Philadelphia 4, Pennsylvania.



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SEPTEMBER 1, 1957

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